Gold(I)-Catalyzed Stereoselective Polycyclizations

Zhouting Rong

UNIVERSITAT
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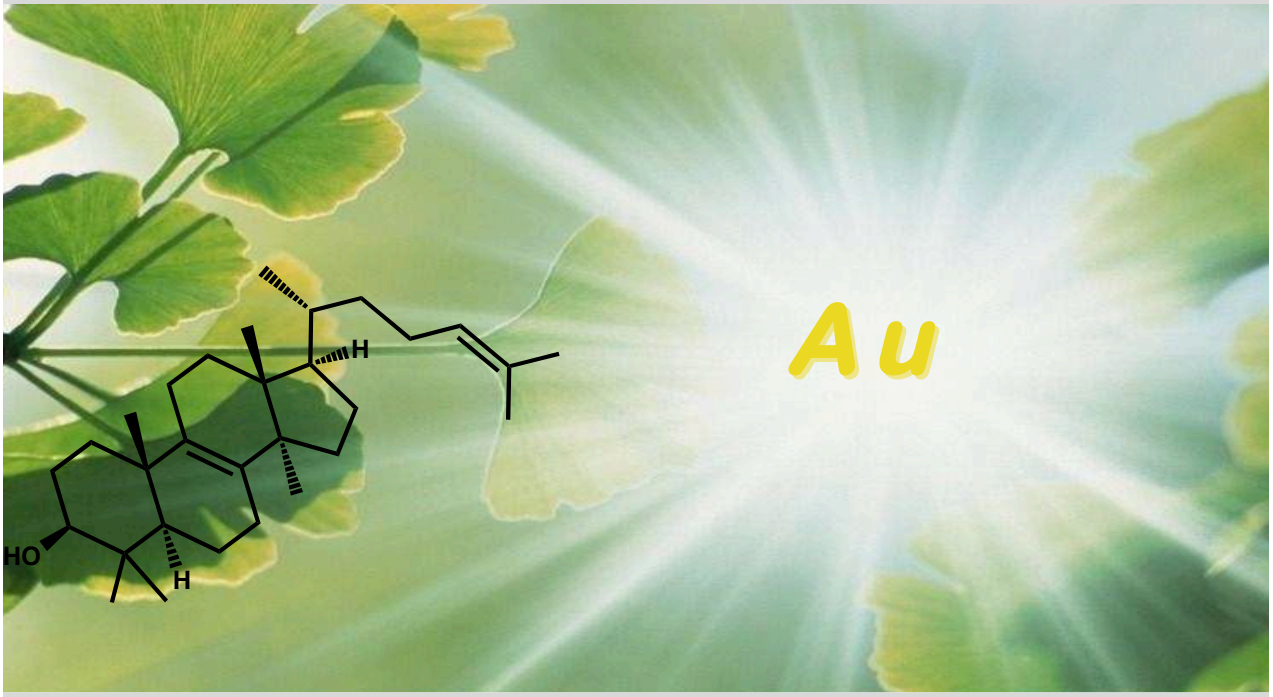

DOCTORAL THESIS
2017

Zhouting Rong

Gold(I)-Catalyzed Stereoselective Polycyclizations

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

UNIVERSITAT ROVIRA I VIRGILI

Tarragona
2017

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HAGO CONSTAR que este trabajo de investigación titulado "Gold(I)-Catalyzed Stereoselective Polycyclizations", que presenta Zhouting Rong para la obtención del título de doctor, ha sido realizado bajo mi dirección en el Institut Català d'Investigació Química vinculado a la Universidad Rovira I Virgili.

Tarragona, 16 de marzo de 2017

El director de la Tesis Doctoral

Prof. Antonio M. Echavarren

To my family and my friends.

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At the moment of writing this Thesis, the results presented herein had been published in:

"Broad Scope Gold(I)-Catalysed Polyenyne Cyclisations for the Formation of up to Four Carbon-Carbon Bonds"

Zhouting Rong and Antonio M. Echavarren, *Org. Biomol. Chem.* **2017**, *15*, 2163−2167.

Other work that were not presented in this Thesis were published in:

"Formal (4+1) Cycloaddition of Methylencyclopropanes with 7-Aryl-1,3,5-cycloheptatrienes by Triple Gold(I) Catalysis"

Yahui Wang, Michael E. Muratore, Zhouting Rong, and Antonio M. Echavarren, *Angew. Chem. Int. Ed*. **2014**, *53*, 14022−14026. This paper is attached at the end of the Thesis.

"Gold, Chloro[dicyclohexyl[2′ ,4′ ,6′ -tris(1-methylethyl)[1,1′ -biphenyl]-2-yl]phosphine]"

Zhouting Rong and Antonio M. Echavarren, *Encyclopedia of Reagents for Organic Synthesis,* Wiley, 2016.

Previous Publication

The work during my Master period had been published in:

"Reagent-free Synthesis of 2,3,4-Polysubstituted Tetrahydroquinolines: Application to the Formal Synthesis of (±)-Martinellic Acid and Martinelline"

Zhouting Rong, Qingjiang Li, Wenhan Lin, and Yanxing Jia, *Tetrahedron Lett*. **2013**, *54*, 4432−4434.

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Prologue

This thesis has been divided into one general introduction, one general objective, two research chapters and an overall conclusion. Each chapter contains an individual background, an objective. Afterwards, the results are presented and discussed leading to a conclusion.

◆ The introduction provides a background and some methods that have been developed for the biomimetic polycyclizations of polyenes.

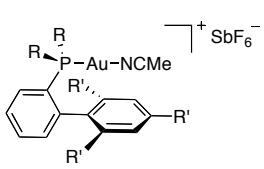
◆ Chapter 1 presents the scope of gold(I)-catalyzed polycyclization of 1,5,n-polyenynes. All successful and unsuccessful examples are presented. Part of this work is included in the following publication: Zhouting Rong and Antonio M. Echavarren, *Org. Biomol. Chem.* **2017**, *15*, 2163−2167.

◆ Chapter 2 presents the exploration of asymmetric gold(I)-catalyzed polycyclization. This part of work is still unpublished.

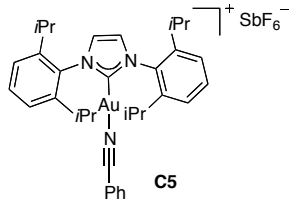
◆ The appendix contains the paper of the collaborative work with Dr. Yahui Wang and Dr. Michael Muratore on a new cycloaddition via gold carbenes that was published in 2014.

List of Catalysts, Abbreviations and Acronyms

All of the gold(I) complexes used in this thesis have been listed bellow. They were prepared according to our previous publications.[1]



C1: R = *t*-Bu, R' = H
C2: R = *t*-Bu, R' = *i*-Pr
C3: R = Cy, R' = H
C4: R = Cy, R' = *i*-Pr



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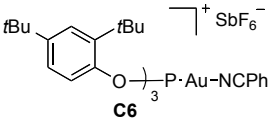


C6

In this manuscript, the abbreviations and acronyms used follow the recommendations found in the on-line "Guidelines for authors" *J. Org. Chem*. **2006**, *71*, 1A−11A.

1 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148. (b) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029–6032. (c) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721–7730. (d) M. Raducan, PhD thesis, ICIQ, 2010.

General Introduction

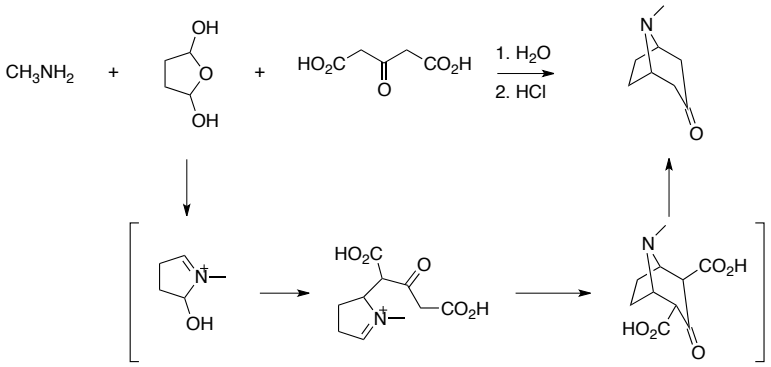
Biomimetic Synthesis

Nature has developed a wide diversity of biochemical pathways to construct complex molecules, which has inspired chemists to use biomimetic strategies in their synthetic approaches. Thus, a synthetic approach to a natural product is considered a biomimetic synthesis when it imitates a well-established or proposed biosynthetic pathway, which means that the reactions carried out and the intermediate structures are closely related to those that occur in the biosynthesis in the natural compound. On the other hand, to test a biosynthetic hypothesis, the execution of a series of reactions to parallel the proposed biosynthesis can also be considered a biomimetic synthesis.

The first biomimetic synthesis was demonstrated by Sir Robert Robinson in his 1917 paper describing his synthesis of tropinone from methyl amine, succinaldehyde, and acetone dicarboxylic acid (Scheme 1).[2] Since then, the number of reported biomimetic synthesis has increased, especially in the last twenty years. Biomimetic strategies often feature high efficiency since they allow the construction of complex natural products in a minimum of steps with simple reagents and afford sufficient quantities of target molecules and intermediates for biological research.[3]

2 Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762−768.

3 Selected reviews on biomimetic synthesis: (a) Johnson, W. S. *Angew. Chem. Int. Ed.* **1976**, *15*, 9. (b) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349−366. (c) Stocking, E. M.; Williams, R. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3078−3115. (d) de la Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 160−181. (e) Poupon, E.; Nay, B. *Biomimetic Organic Synthesis*, Wiley-VCH, Weinheim, Germany, **2011**, doi: 10.1002/9783527634606.



Scheme 1. Biomimetic Synthesis of Tropinone by Robinson

Polyene Cyclizations

Polyene cyclizations are the most emblematic examples of biomimetic synthesis since they allow the formation of several carbocycles with contiguous stereocenters in a single step.

The polyene cyclization was discovered by Bloch and Rittenberg in 1945 when they conducted isotope labeling experiments in mice and found that both squalene and cholesterol derive from acetic acid.[4] Based on their discovery, Bloch and Rittenberg hypothesized that squalene might be the actual precursor for cholesterol. Since then, numerous studies have been carried out by scientists to understand the biosynthesis of squalene, cholesterol, and their derivatives.[5]

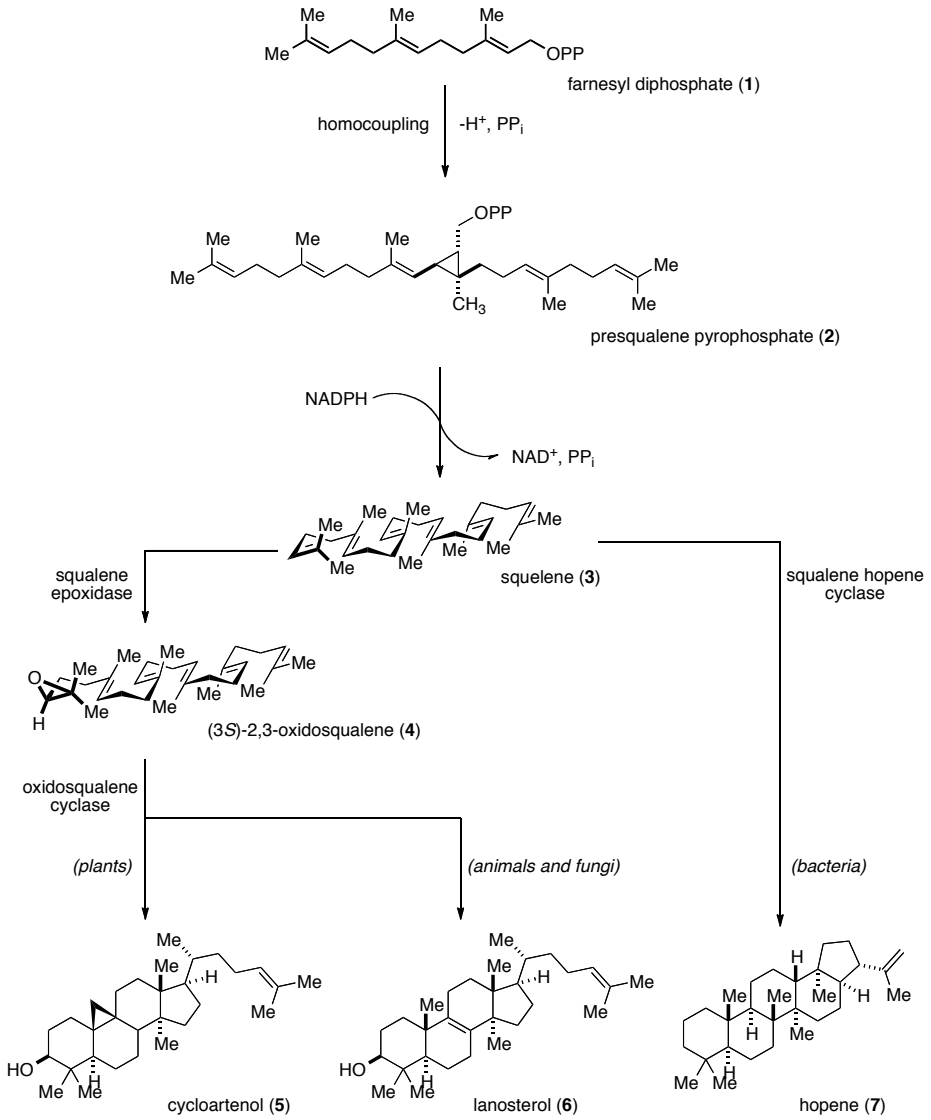
The first step of steroid biosynthesis is the generation of squalene (**3**) by the squalene synthase-catalyzed homocoupling of farnesyl diphosphate (**1**) via presqualene pyrophosphate (**2**).[6] It is followed by an enantioselective epoxidation with squalene epoxidase to generate (3*S*)-2,3-oxidosqualene (**4**). There are numerous oxidosqualene cyclases in Nature to transfer (3*S*)-2,3-oxidosqualene into polycyclic products. Each cyclase affords a unique product such as cycloartenol (**5**) in plants and lanosterol (**6**) in

4 Bloch, K.; Rittenberg, D. *J. Biol. Chem*. **1945**, *159*, 45−58.

5 Selected reviews on biosynthesis of steroids: (a) Giner, J.-L. *Chem. Rev*. **1993**, *93*, 1735−1752. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev*. **2005**, *105*, 4730−4756.

6 (a) Dewar, M. J.; Ruiz, J. M. *Tetrahedron* **1987**, *43*, 2661−2674. (b) Jarstfer, M. B.; Blagg, B. S. J.; Rogers, D. H.; Poulter, C. D. *J. Am. Chem. Soc*. **1996**, *118*, 4730−4756.

animals and fungi. In contrast, in bacteria, epoxidation of squalene does not happen. Rather, an enantioselective, diastereoselective polycyclization catalyzed by squalene-hopene cyclase converts squalene into hopene (**7**) (Scheme 2).[7]



Scheme 2. Biosynthesis Pathways Involving Squalene and Oxidosqualene Cyclases

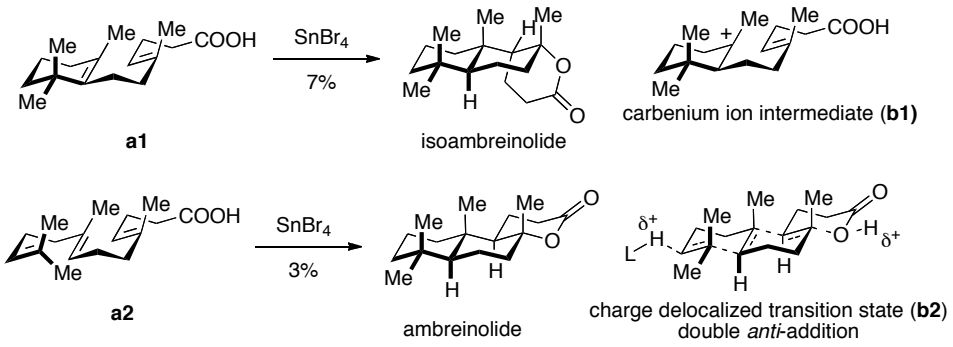
7 (a) Ourisson, G.; Rohmer, M.; Poralla, K. *Annu. Rev. Microbiol.* **1987**, *41*, 301−333. (b) Kannenberg, E. L.; Poralla, K. *Naturwissenschaften* **1999**, *86*, 168−176.

The biosynthesis of steroids features everything that a chemist wants to take place in a flask. Natural abundant (cheap and readily available) starting materials are used in these biochemical transformations which produce valuable bioactive molecules (synthetically useful). The transformation is highly efficient since usually several bonds and rings are formed in a single step with high atom economy. Remarkably, excellent diastereoselectivities and enantioselectivities are achieved.

Chemists were inspired by the biosynthesis of steroids and many polyene cyclization reactions were developed in the past seventy years, especially in the last two decades when enantioselective methods were widely employed.

Stork and Eschenmoser's Hypothesis

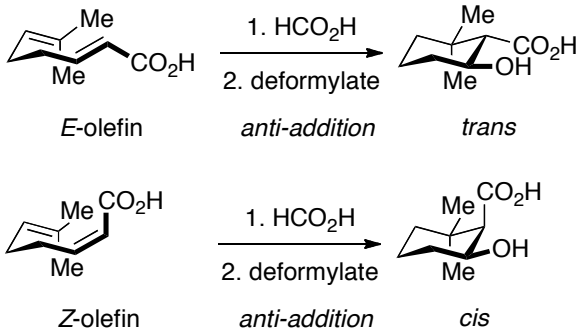
Stork and Eschenmoser's hypothesis, which was proposed in 1955, is perhaps the most important rule that is followed by chemists working on polyene cyclization.[8] Stork reasoned that since naturally occurring triterpenes and steroids are mostly *trans-anti-trans* structures, they may be formed by concerted cyclization of polyenes rather than by step-wise cyclizations, a path which would lead to *cis* relative configuration. The hypothesis was supported by the cyclization of **a1** and **a2** in the presence of $SnBr_4$ as the Lewis acid. Substrate **a1** produced isoambreinolide in 7% yield, clearly proceeding via carbenium ion (**b1**). In contrast, **a2** gave rise to ambreinolide, presumably as a single diastereomer, in 3% yield. This result indicated that the cyclization of **a2** might be concerted, involving a single transition state **b2**. If the cyclization of **a2** would have taken place step-wise, isoambreinolide would have probably been formed (Scheme 3).



Scheme 3. Stork's Cyclization of Farnesyl Acetic Acid

8 (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc*. **1955**, *77*, 5068−5077. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904.

Eschenmoser and Schinz subjected geometric isomers of norgeranic acid to cyclization in formic acid. Subsequent saponification of the formate ester produced a single diastereomer in each case, indicating a stereospecific reaction of a concerted *anti* addition to the 1,5-diene (Scheme 4).



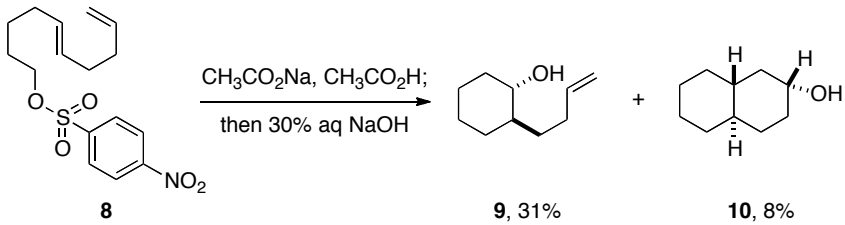
Scheme 4. Schinz-Eschenmoser Evidence for Concerted *anti*-Addition to an Olefin

Johnson's Contribution

Among all the chemists that have made contributions to developing methodologies of polyene cyclizations in the last century, William S. Johnson stands out for his continuous efforts on discovering new polyene cyclization reactions and mechanistic investigations. Herein, some selected discoveries by Johnson are presented.

In 1964, Johnson reported the solvolysis of *trans*-5,9-decadienyl *p*-nitrobenzenesulfonate (**8**) in 100% acetic acid containing 2 mole equiv of sodium acetate.[9] Although the main product obtained was the monocyclic compound, the decalol **10** was still formed in 8% yield (Scheme 5). It is noteworthy that **10** was obtained as a single diastereomer whose configuration is in accordance with the Stork and Eschenmoser's hypothesis.

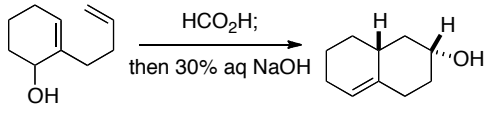
9 Johnson, W. S.; Bailey, D. M.; Owyang, R.; Bell, R. A.; Jaques, B.; Crandall, J. K. *J. Am. Chem. Soc*. **1964**, *86*, 1959−1966.



8 **9**, 31% **10**, 8%

Scheme 5

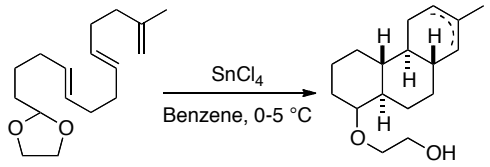
In the same year, Johnson reported a more efficient polyene cyclization reaction.[10] A more reactive substrate **11** was dissolved in anhydrous formic acid at room temperature and essentially all of the starting material was consumed in less than 5 min. Vapor phase chromatography analysis and quantitative peak area comparison experiments showed that the yield of octalol **12** was between 80 and 92% (Scheme 6).



11 80-92% **12**

Scheme 6

In 1966, Johnson reported the first example of the stereoselective polyene cyclization of a tricarbocyclic system. A dilute solution of acetal **13** in benzene was treated with 1 mole equiv of stannic chloride at 0-5 °C for 17 min to give an 89% yield of monohydric alcohol which consisted mainly of the tricyclic unsaturated alcohols **14** (Scheme 7).[11] In addition to its theoretical significance, this finding promised to have synthetic utility.



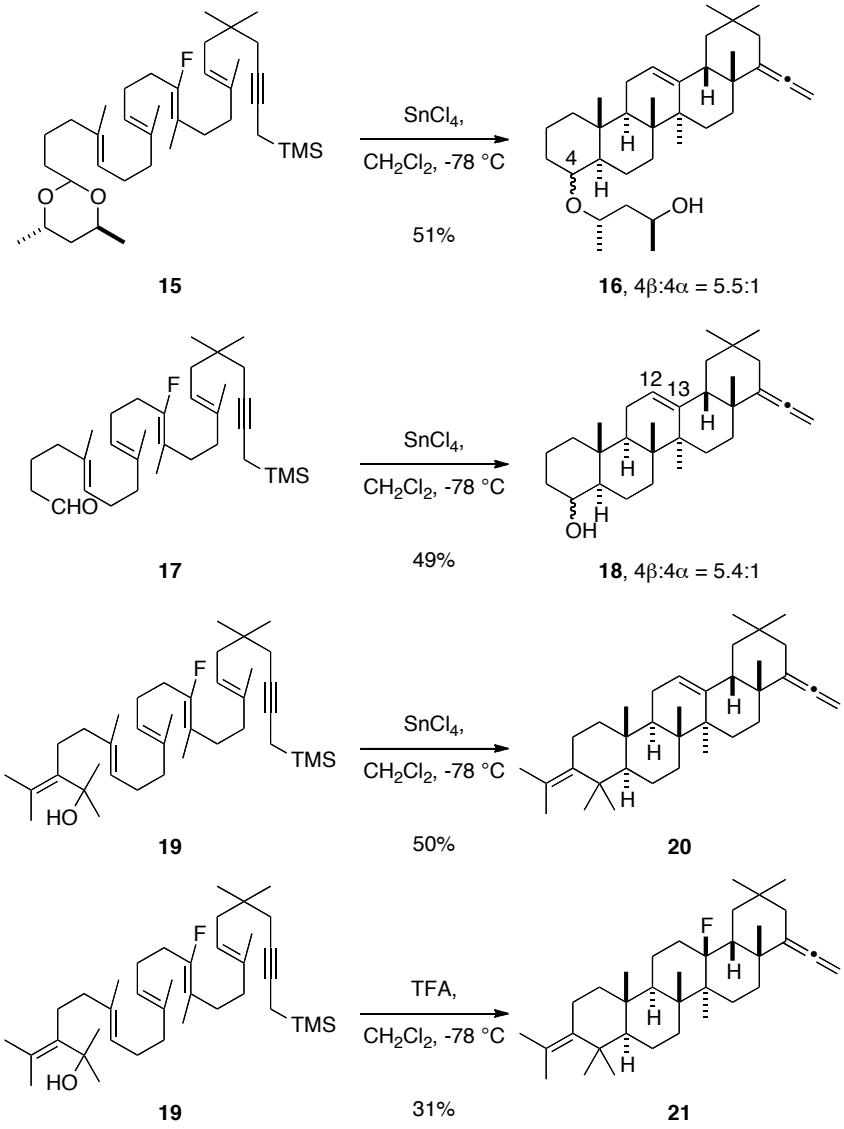
13 89% **14**

Scheme 7

10 Johnson, W. S.; Lunn, W. H.; Fitzi, K. *J. Am. Chem. Soc*. **1964**, *86*, 1972−1978.
11 Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc*. **1966**, *88*, 3861−3862.

In 1994, the first example of nonenzymatic polyene pentacyclization was achieved by the group of Johnson.[12] Polyene acetal **15** was treated with $SnCl_4$ (3.0 equiv, CH_2Cl_2, -78 °C, 10 min) to give a mixture of C4 isomeric pentacycle alcohol **16** in 51% yield (4β:4α = 5.5:1). The F-substituent in this substrate stabilizes the carbocation to bias for six-membered ring formation as well as to promote complete cyclization. Cyclization of polyene aldehyde **17** under identical conditions also afforded a mixture of alcohols **18** (4β:4α = 5.4:1) in 49% yield, again with regioselective *in situ* dehydrofluorination at the C12-13 position. Treatment of allylic alcohol **19** under the previous conditions resulted in facile cyclization with loss of HF to generate pentacycle **20** in 50% yield. In comparison, cyclization of **19** under protic acid conditions (1% trifluoroacetic acid in CH_2Cl_2, -78 °C, 15 min) gave the fluoropentacycle **21** in 31% isolated yield and no dehydrofluorinated product was observed (Scheme 8).

12 Johnson, W. S.; Fish, P. V. *J. Org. Chem.* **1994**, *59*, 2324−2335.



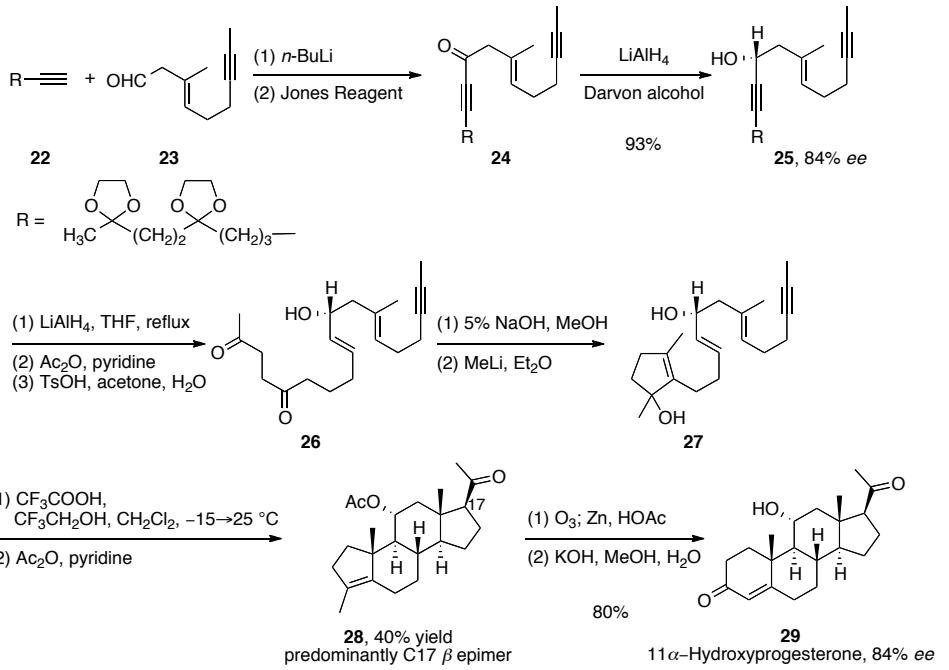
Scheme 8

Johnson also applied these polycyclization methods for the total synthesis of some steroids. In 1977, his group reported the asymmetric total synthesis of 11α-hydroxyprogesterone (**29**).[13] The synthesis started with readily available compounds **22** and **23**.[14] The asymmetric reduction of

13 Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc*. **1977**, *99*, 8341−8343.

14 Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc*. **1976**, *98*, 1039−1041.

the acetylenic ketone **24** with the complex generated from $LiAlH_4$ and Darvon alcohol[15] afforded the chiral propargylic alcohol **25** in 84% *ee*. Substrate **27** was converted into a tetracyclic compound by exposing to trifluoroacetic acid, which was then acetylated to give **28** as a mixture of 17β and 17α epimers, favoring the 17β-isomer. Finally, ozonolysis followed by intramolecular aldol reaction affored 11α-hydroxyprogesterone (**29**) (Scheme 9).



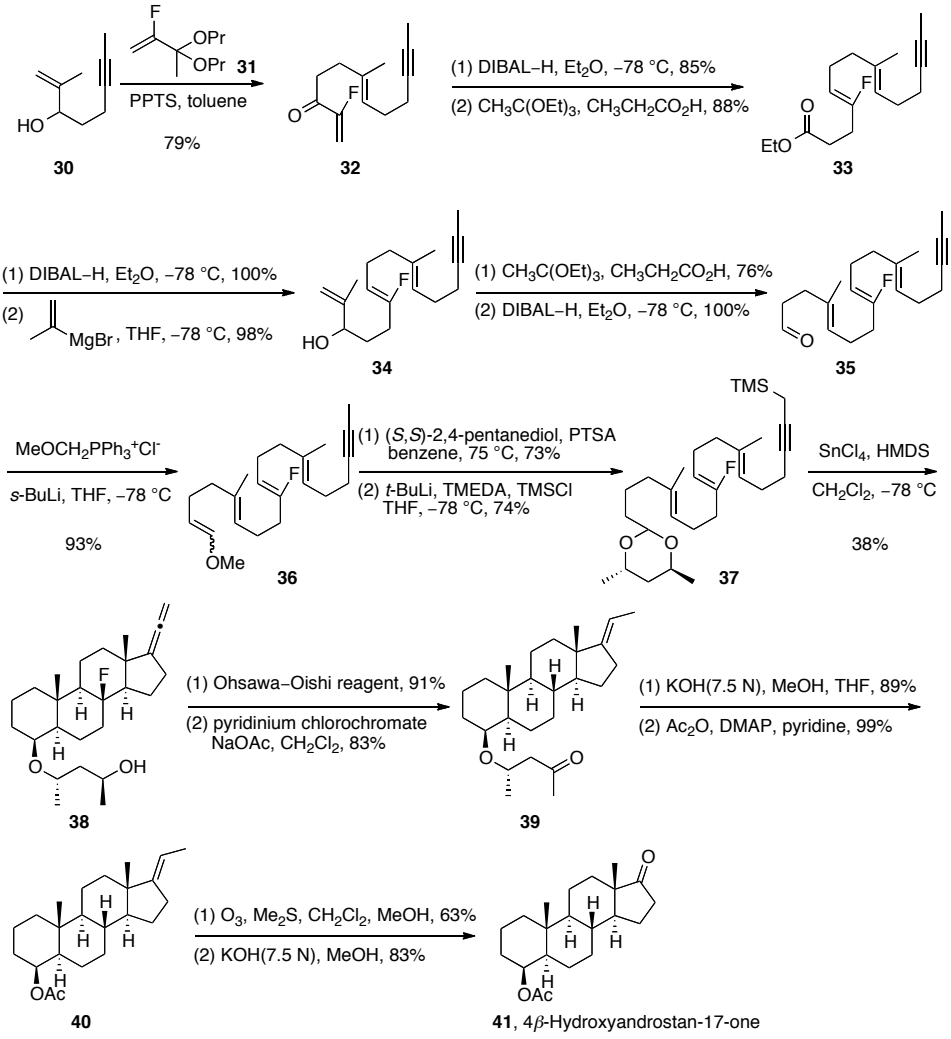
Scheme 9. Asymmetric Total Synthesis of 11α-Hydroxyprogesterone

In 1993, Johnson reported the asymmetric total synthesis of 4β-hydroxyandrostan-17-one (**41**) by means of a polyene cyclization strategy using a fluorine atom as a cation-stabilizing auxiliary.[16] The cyclization substrate **37** could be synthesized with the correct configuration by a series of Claisen rearrangements starting from two readily available

15 (a) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870−1877. (b) Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339−8341.

16 Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497−504.

compounds **30** and **31** (Scheme 10).[17] The polyene cyclization of *S*,*S* acetal **37** in the presence of $SnCl_4$ and hexamethyldisiloxane in −78 °C gave fluorotetracycle **38** as the major product in 38% yield. The fluorinated cyclized compound was converted to 4*β*-hydroxyandrostan-17-one (**41**) in six additional steps.



Scheme 10. Asymmetric Total Synthesis of 4*β*-Hydroxyandrostan-17-one

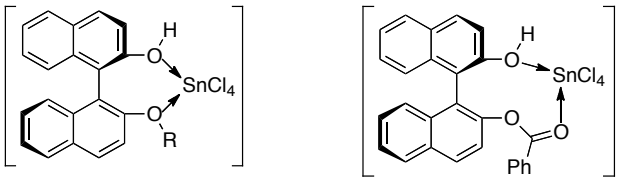
17 Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc*. **1971**, *93*, 4332−4334.

Recent Advances in Polyene Cyclizations

In the last two decades, many other polyene cyclization reactions have emerged, with a particular focus on the application of catalytic asymmetric methods. Some representative works can be divided into four types: i. Brønsted acid catalysis, ii. halonium-induced polyene cyclizations, iii. organocatalysis and iv. transition metal catalysis.

Brønsted Acid Catalyzed Polyene Cyclizations

In 1999, Yamamoto and co-workers reported the first enantioselective biomimetic polyene cyclization.[18] The combined system of a Lewis acid and a chiral Brønsted acid, which was called LBA, was designed as an artificial cyclase. These LBAs can be prepared from $SnCl_4$ and optically active 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) derivatives (Figure 1).

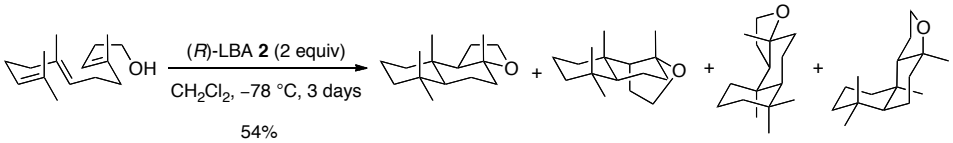


LBA **1** (R=H)
LBA **2** (R=Me)
LBA **3** (R= *i*-Pr)

LBA **4**

Figure 1

Homofarnesol (**42**) was chosen to test the reactivity of LBA. When exposed to 2 mole equiv of (*R*)-LBA **2** in CH_2Cl_2 at −78 °C for 3 days, homofarnesol (**42**) yielded 54% of the tricyclic product with moderate enantioselectivity and diastereoselectivity (Scheme 11).



42

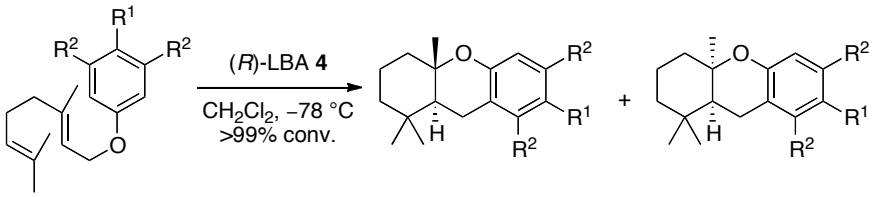
43 56 (42% ee) : **44** 9 : **45** 26 (20% ee) : **46** 9

Scheme 11

18 Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc*. **1999**, *121*, 4906−4907.

It was proposed that the hydroxy group in homofarnesol (**42**) inhibited the catalytic activity of LBAs so the more reactive geranyl phenyl ether **47** was employed to investigate the cyclization system further (Table 1).[19] When stoichiometric amount of (*R*)-LBA **4** was used, the cyclized products could be obtained in good yields and moderate enantioselectivities after 1 day. Reducing the amount of (*R*)-LBA **4** resulted in slower conversion of **47** but higher enantioselectivities.

Table 1. Enantioselective Cyclization of Geranyl Aryl Ether 47



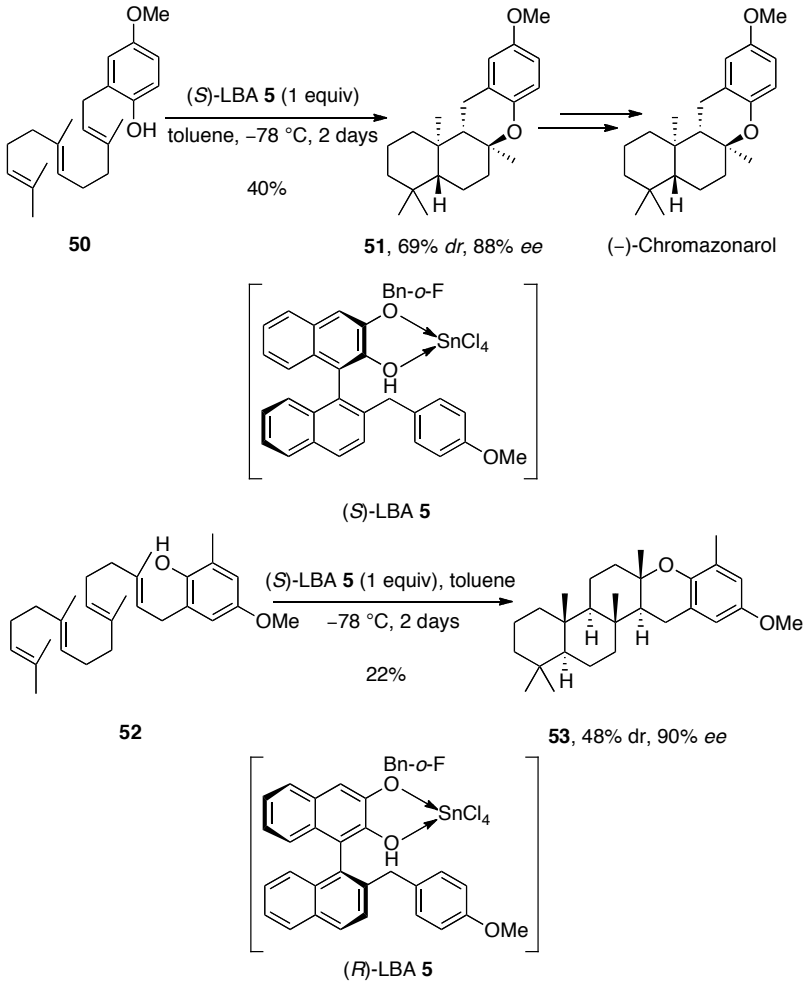
47 (–)-**48** **49**

Entry	**47**		(*R*)-LBA **4** (equiv)	time (day)	**48**		ratio **48**:**49**
	R^1	R^2			GC yield (%)	ee (%)	
1	H	H	1.1	1	98	69	98:2
2	H	H	0.2	4	98	77	98:2
3	F	H	1.1	1	98	63	94:6
4	F	H	0.2	4	72	79	70:30
5	Cl	H	1.1	1	99	65	98:2
6	Cl	H	0.2	4	97	82	97:3
7	Br	H	1.1	1	87	63	94:6
8	Br	H	0.2	4	85	87	89:11
9	Br	H	0.15	6	94	90	95:5
10	Me	H	1.1	1	92	62	95:5
11	Me	H	0.2	4	94	67	97:3
12	OMe	H	1.1	1	84	70	95:5
13	OMe	H	0.2	4	92	42	94:6
14	H	Me	1.1	1	80	62	89:11
15	H	Me	0.2	4	82	46	91:9

The group of Yamamoto also applied this methodology to the total synthesis of (−)-Chromazonarol and **53**, a synthetic analogue of (−)-taondiol.[20] Still, stoichiometric LBAs had to be used to promote the polyene cyclizations in toluene at −78 °C for 2 days. The reactions provided the cyclic products in good enantioselectivities and low yields (Scheme 12).

19 Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131−8140.

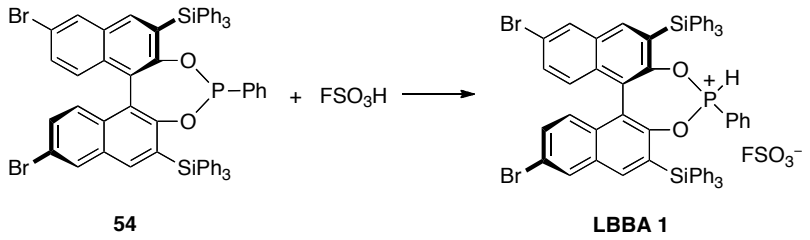
20 Ishihara, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122−11123.



Scheme 12

In 2011, Ishihara and co-workers reported a chiral Lewis base-assisted Brønsted acid (LBBA)-catalyzed enantioselective cyclization of 2-geranylphenols.[21] The catalyst (LBBA **1**) is a phosphonium salt which was generated by mixing chiral phosphorus compound **54** with fluorosulfonic acid (Scheme 13).

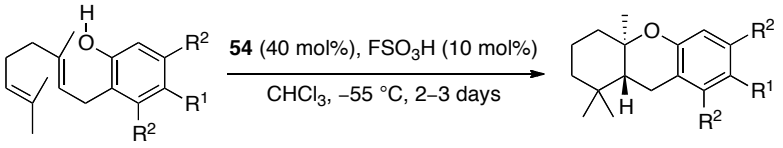
21 Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett*. **2011**, *13*, 3130−3133.



54 **LBBA 1**

Scheme 13

The 2-geranylphenols underwent the desired cyclization with LBBA **1** prepared *in situ* in $CHCl_3$ at −55 °C for 2−3 days to afford **56** in reasonable yields with good *trans/cis*-selectivities and good enantioselectivities (Scheme 14).



55 *trans*-**56**

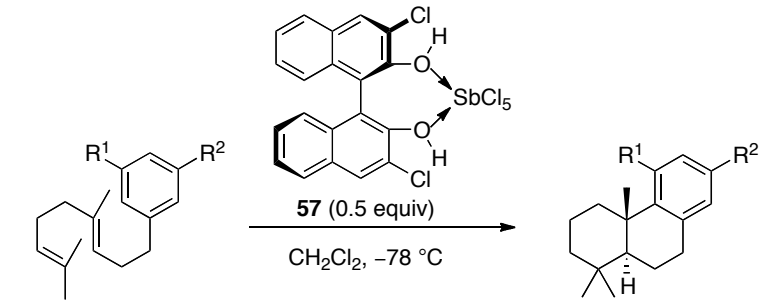
55a: R^1=Me, R^2=H
55b: R^1=OMe, R^2=H
55c: R^1=I, R^2=H
55d: R^1=H, R^2=Me

56a: 64%, *trans/cis*=90:10, 93% *ee*
56b: 43%, *trans/cis*=96:4, 88% *ee*
56c: 48%, *trans/cis*=97:3, 87% *ee*
56d: 44%, *trans/cis*=91:9, 88% *ee*

Scheme 14

In 2012, Corey and Surendra reported another LBA promoted polyene cyclization.[22] Instead of $SnCl_4$, these authors used $SbCl_5$ as the Lewis acid, which was proposed to help improving the enantioselectivity and terminal C=C selectivity of cation−polyolefin cyclization since it is a bulkier and stronger Lewis acid than $SnCl_4$. Thus, catalyst **57**, a 1:1 complex of 2,2'-dichloro-BINOL and $SbCl_5$, was employed to promoted the cyclizations of **58** in CH_2Cl_2 at −78 °C (Scheme 15). The reactions occurred rapidly when 0.5 equivalent of **57** was used and good yields and good enantioselectivities were obtained.

22 Surendra, K.; Corey, E. J. *J. Am. Chem. Soc*. **2012**, *134*, 11992−11994.



58

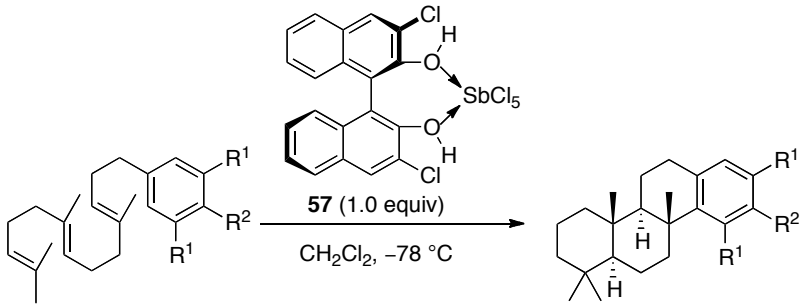
58a: R^1=R^2=H
58b: R^1=R^2=OMe
58c: R^1=H, R^2=Br
58d: R^1=H, R^2=OSi(*t*-Bu)$_2$*i*-Bu

59

59a: 80%, 91% *ee*
59b: 85%, 87% *ee*
59c: 82%, *para*:*ortho*=4:1, 90% *ee*
59d: 89%, *para*:*ortho*=9:1, 92% *ee*

Scheme 15. Lewis Acid 57 Promoted Bicyclization in CH_2Cl_2

Tricyclization reactions were also tested by using 1 equiv of **57** in CH_2Cl_2 at −78 °C (Scheme 16).



60

60a: R^1=R^2=H
60b: R^1=OMe, R^2=H
60c: R^1=H, R^2=OSi(*t*-Bu)$_2$*i*-Bu

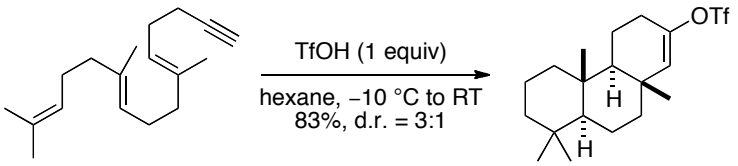
61

61a: 70%, 90% *ee*
61b: 76%, 84% *ee*
61c: 74%, *para*:*ortho*=9:1, 90% *ee*

Scheme 16. Lewis Acid 57 Promoted Tricyclization in CH_2Cl_2

In 2015, the group of Rodríguez reported a triflic acid (TfOH)-mediated biomimetic cationic cyclization (Scheme 17).[23] No metallic reagent is needed in this transformation and the cyclic alkenyl triflate product is a useful intermediate in organic synthesis.

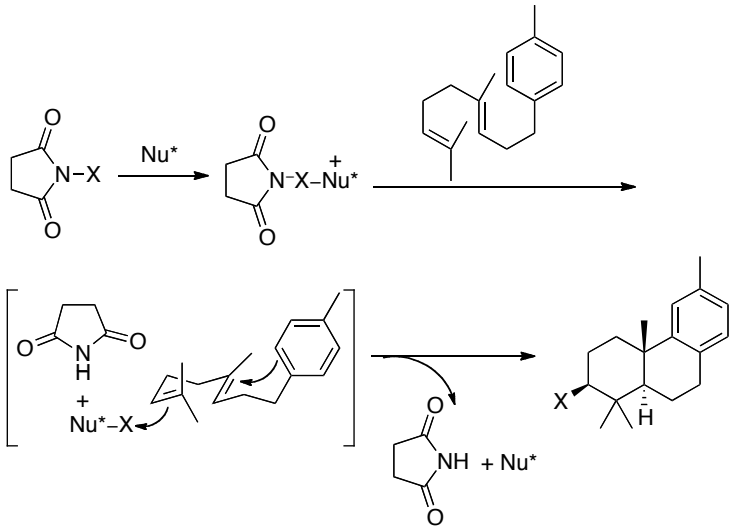
23 Alonso, P.; Pardo, P.; Galván, A.; Fañanás, F. J.; Rodríguez, F. *Angew. Chem., Int. Ed*. **2015**, *54*, 15506−15510.



Scheme 17. Triflic Acid-Mediated Cationic Cyclization

Halonium-Induced Polyene Cyclizations

In 2007, Ishihara and co-workers reported an enantioselective halocyclization induced by nucleophilic phosphoramidites.[24] This group proposed that a halogenating reagent could be attacked by a nucleophile (Nu*) to generate an activated halogen atom (X) that could serve as an initiator for the polycyclization. If the nucleophile could provide a chiral environment for the halogen atom, good enantioselectivities could be achieved since the activated halogen atom was placed close to the chiral nucleophilic promoter (Scheme 18).

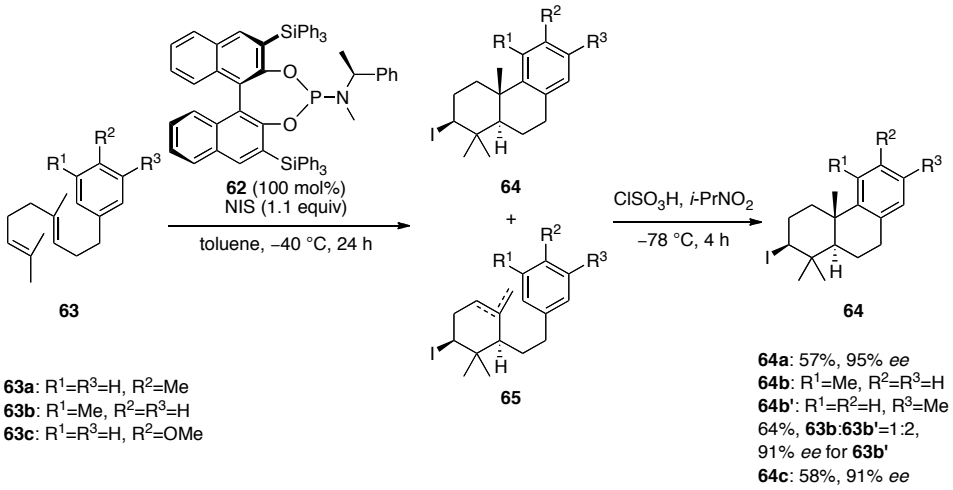


Scheme 18. Nucleophilic Promoters for the activation of *N*-halosuccinimides and Halocyclization of 4-(homogeranyl)toluene

Chiral phosphoramidite **62** was found to be the most effective nucleophilic promoter for this transformation. When 100 mol% of **62** was used in toluene at −40 °C for 24 h with *N*-iodosuccinimide, substrate **63** gave bicyclic product **64** and monocyclized product **65**, which upon

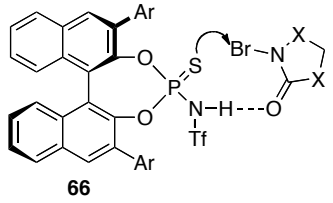
24 Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900−903.

treatment of chlorosulphonic acid, afforded **64** in excellent enantioselectivities and moderate yields (Scheme 19).



Scheme 19. Enantioselective Iodocyclizations Induced by Chiral Nucleophilic Promoter 62

Recently, the Yamamoto group achieved the first catalytic asymmetric bromonium ion-induced polyene cyclization by using a chiral BINOL-derived thiophosphoramide catalyst (**66**) and 1,3-dibromo-5,5-dimethylhydantoin (**67**) as the bromide source.[25] Catalyst **66** served both as a Lewis base to activate the bromide atom and a Brønsted acid to activate the carbonyl group in the brominating reagent (Figure 2).



66

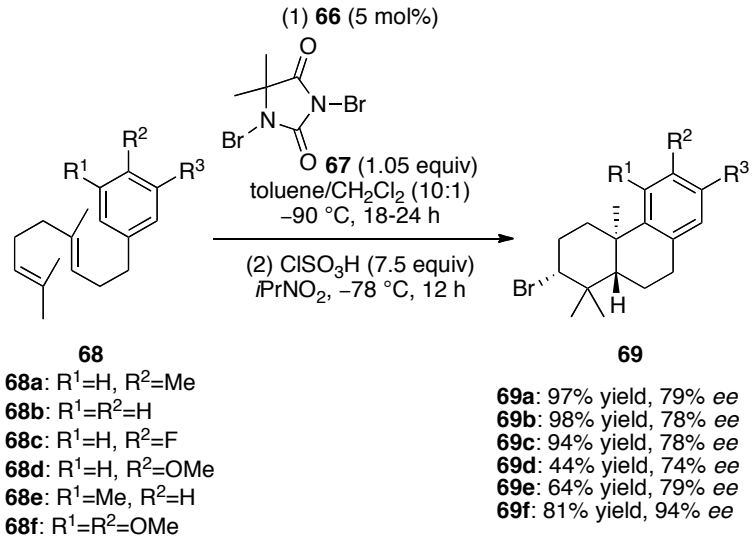
Ar=2,6-*i*Pr$_2$-4-(9-anthracenyl)C$_6$H$_2$

Figure 2

Thus, the cyclization substrates were treated with **66** (5 mol%) and **67** (1.05 equiv) in toluene and CH_2Cl_2 at −90 °C for 18-24 h (Scheme 20). The crude reaction mixture was treated with chlorosulfonic acid to convert some partially cyclized products into the fully cyclized products

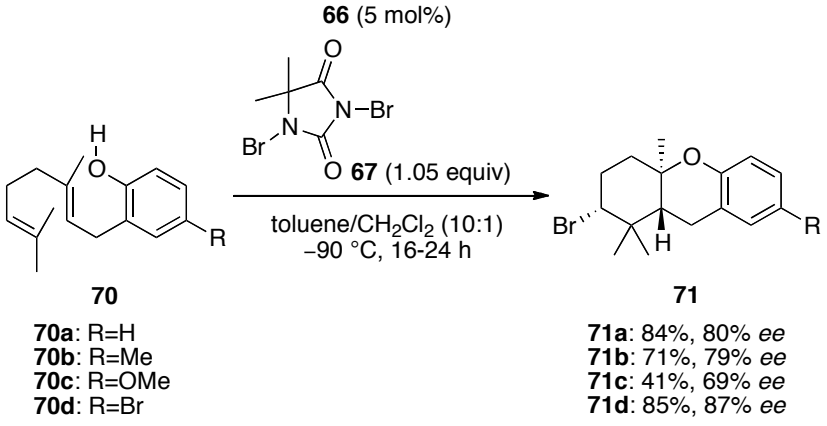
25 Samanta, R. C.; Yamamoto, H. *J. Am. Chem. Soc*. **2017**, *139*, 1460−1463.

69 in moderate to excellent yields and moderate to excellent enantioselectivities.



Scheme 20. Scope of Bromocyclization for Homogeranylbenzenes

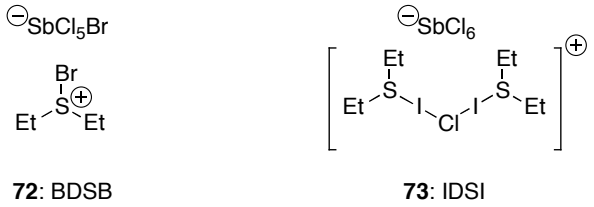
Likewise, 4-substituted geranylphenols **70** were converted into the bromocyclization products with good yields and enantioselectivities (Scheme 21).



Scheme 21. Bromocyclization of Geranylphenols

In 2009 and 2010, Snyder and co-workers reported the development of BDSB (bromodiethylsulfonium bromopentachloroantimonate, **72**) and

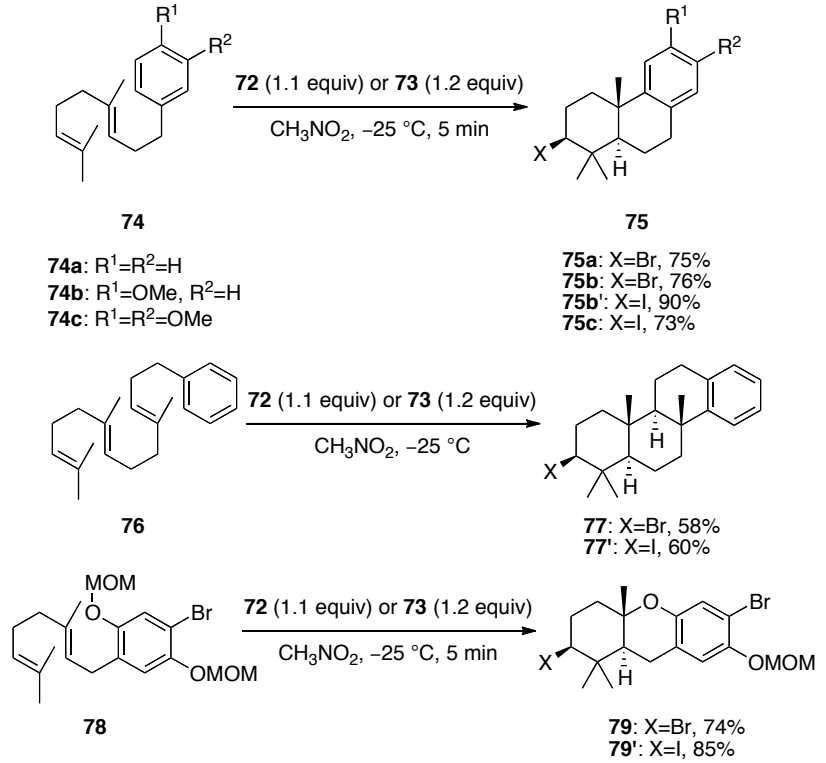
IDSI (**73**) as new halogenating reagents (Figure 3).[26] Both reagents could be prepared by mixing Br_2 or I_2 with diethyl sulfide and $SbCl_5$ in 1,2-dichloroethane at low temperature.



72: BDSB **73**: IDSI

Figure 3

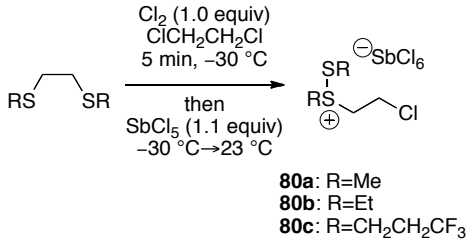
By treatment with **72** or **73** in nitromethane at −25 °C, the cyclization substrates rapidly gave bromocyclized or iodocyclized compounds in good yields and excellent diastereoselectivities (Scheme 22).



Scheme 22. Halonium-Induced Polyene Cyclizations Using BDSB or IDSI

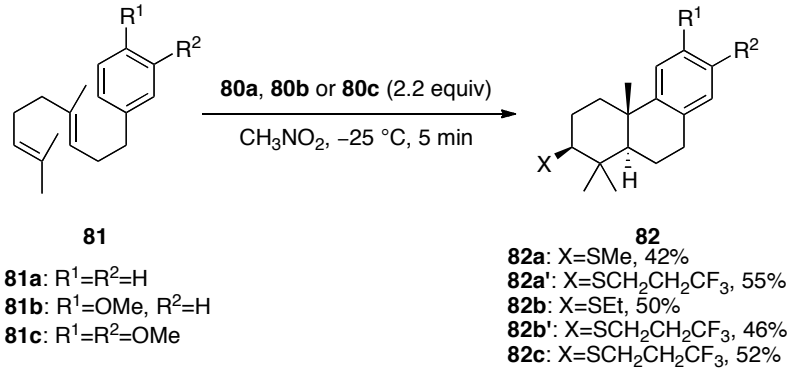
26 (a) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed*. **2009**, *48*, 7899−7930. (b) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc*. **2010**, *132*, 14303−14314.

Sulfonium-induced polyene cyclization could be achieved with reagents that were developed in a similar way.[27] These isolable alkyldisulfanium salts were prepared by exposing the corresponding disulfide to molecular Cl_2 and $SbCl_5$ in 1,2-dichloroethane (Scheme 23).



Scheme 23

These new reagents allowed the installation of −SMe, −SEt and $-SCH_2CH_2CF_3$ in modest yields in the polyene cyclization process (Scheme 24).



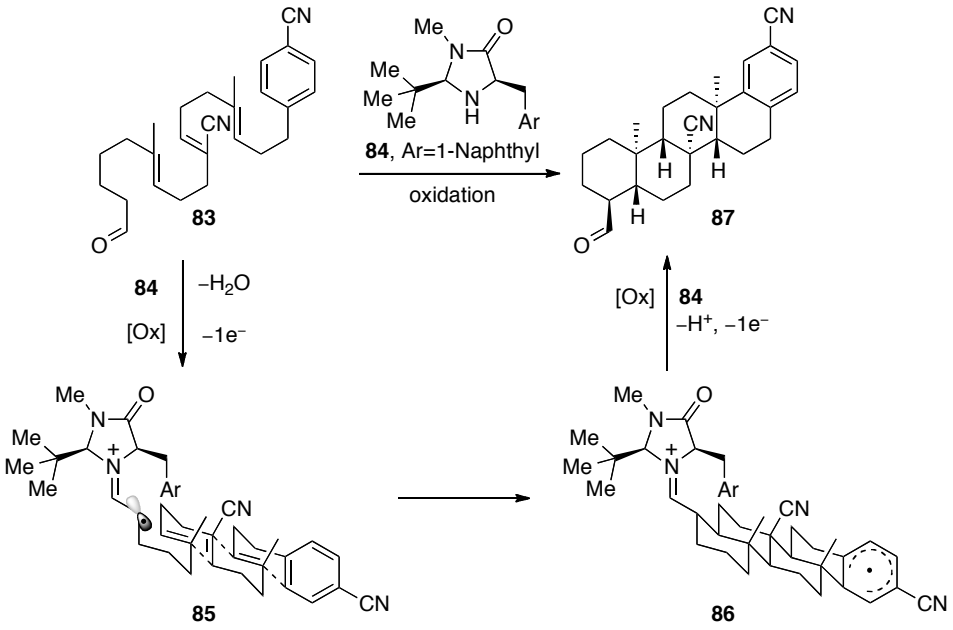
Scheme 24

Organocatalyzed Polyene Cyclizations

In 2010, the MacMillan group reported an organocatalyzed polycyclization via SOMO activation strategy.[28] This group hypothesized that unsaturated aldehyde **83** should condense with imidazolidinone catalyst **84** to give α–imino radical intermediate **85** upon oxidation with an appropriate metal oxidant (Scheme 25). This intermediate would engage in a radical cascade cyclization terminated by a suitable arene to

27 Schevenels, F. T.; Shen, M.; Snyder, S. A. *Org. Lett*. **2017**, *19*, 2−5.
28 Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 5027−5029.

afford cyclohexadienyl radical **86**. Another oxidation would then furnish the corresponding cyclohexadienyl cation, which would deliver the tetracyclized product **87** upon rearomatization and liberation of the catalyst. The α–imino radical intermediate **85** possessed the favored geometry in which the polyene chain was oriented away from the bulky *tert*-butyl substituent and the aryl moiety on the catalyst shielded the *Si* face, leaving the *Re* face exposed to addition across the proximal trisubstituted alkene. Thus, the enantio- and diastereoselectivity could be achieved.

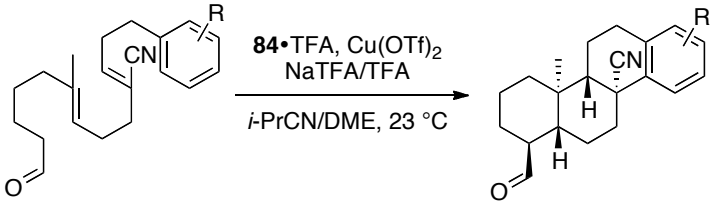


Scheme 25

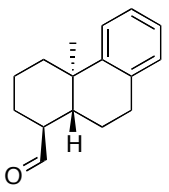
While strong oxidants like cerium(IV) ammonium nitrate (CAN) and $[Fe(phen)_3](PF_6)_3$ that had been successful in other SOMO activation studies could not generate the desired cyclic products, the slow addition of $Cu(OTf)_2$ to a 3:2 mixture of isobutyronitrile with 1,2-dimethoxyethane (DME) with sodium trifluoroacetate (NaTFA) as a base converted the unsaturated aldehydes into the corresponding polycycles in synthetically useful yields and enantioselectivities (Table 2). Bi-, tri-, tetra- and pentacyclizations were obtained using 30 mol% of **84** with good yields and excellent enantiomeric excesses. Up to 6 new C−C bonds,

6 new rings and 11 contiguous chiral centers could be formed in this single transformation.

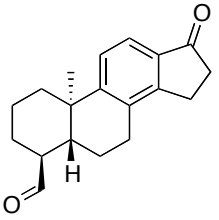
Table 2. Scope Studies in Enantioselective Polyene Cyclization via Organo-SOMO Catalysis



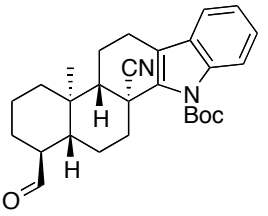
unsaturated aldehyde **enantioenriched polycycle**



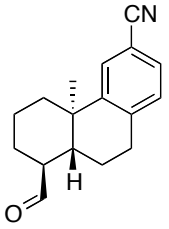
88: 70%, 87% *ee*



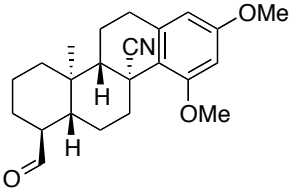
91: 76%, 85% *ee*



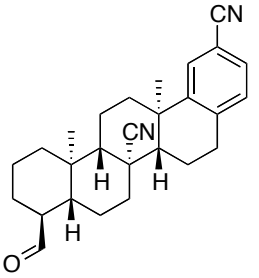
94: 71%, 92% *ee*



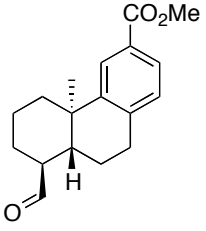
89: 74%, 88% *ee*



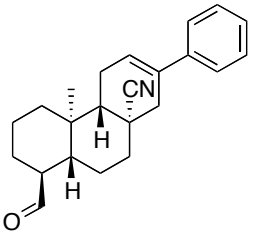
92: 61%, 91% *ee*



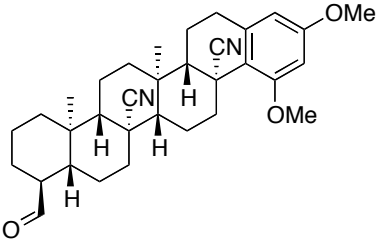
87: 56%, 92% *ee*



90: 77%, 87% *ee*

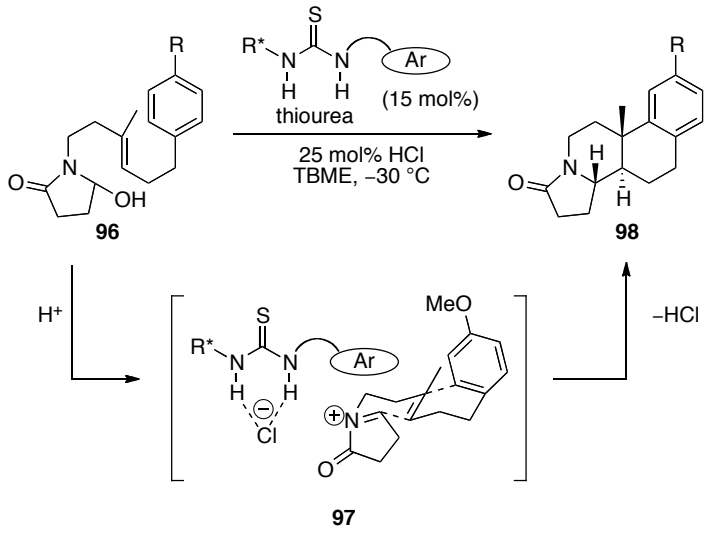


93: 54%, 86% *ee*



95: 63%, 93% *ee*

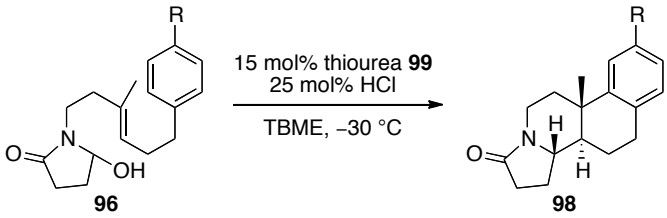
In the same year, Jacobsen and co-workers reported a thiourea-catalyzed polycyclization.[29] Based on their work in anion binding thiourea catalysis, they proposed that treatment of the hydroxylactam substrate **96** with HCl would result in the dehydrative formation of a chlorolactam intermediate (Scheme 26). Hydrogen bond-mediated ionization of this chlorolactam by the thiourea would generate a catalyst-bound iminium•chloride ion pair (**97**) that would undergo cyclization enantioselectively to give tetracyclic product **98**.



Scheme 26. Proposal for Thiourea-Catalyzed Polycyclization

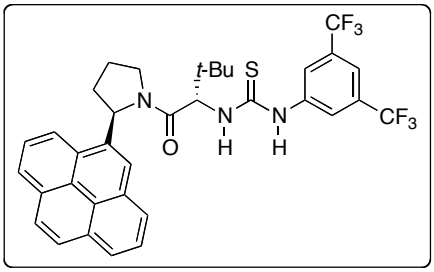
The 4-pyrenyl-substituted thiourea derivative **99** proved to be the optimal catalyst. Thus, different hydroxylactam substrates were exposed to 15 mol% thiourea **99** and 25 mol% HCl in methyl *tert*-butyl ether at −30 °C to furnish bicyclized products in moderate yields and good enantioselectivities (Scheme 27).

29 Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2010**, *132*, 5030−5032.



96a: R=H
96b: R=OMe
96c: R=Me
96d: R=Ph
96e: R=*t*-Bu

98a: 51%, 89% *ee*
98b: 72%, 94% *ee*
98c: 62%, 91% *ee*
98d: 54%, 91% *ee*
98e: 71%, 91% *ee*

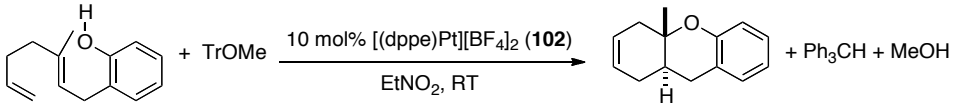


thiourea **99**

Scheme 27

Transition Metal-Catalyzed Polyene Cyclizations

In 2007, the group of Gagné reported a platinum catalyzed oxidative polyene cyclization processes by a trityl cation-mediated hydride abstraction pathway.[30] Treatment of substrate **100** with 10 mol% of $[(dppe)Pt][BF_4]_2$ and stoichiometric polystyrene resin bound trityl methyl ether in $EtNO_2$ furnished the tricyclic product **101** (Scheme 28).

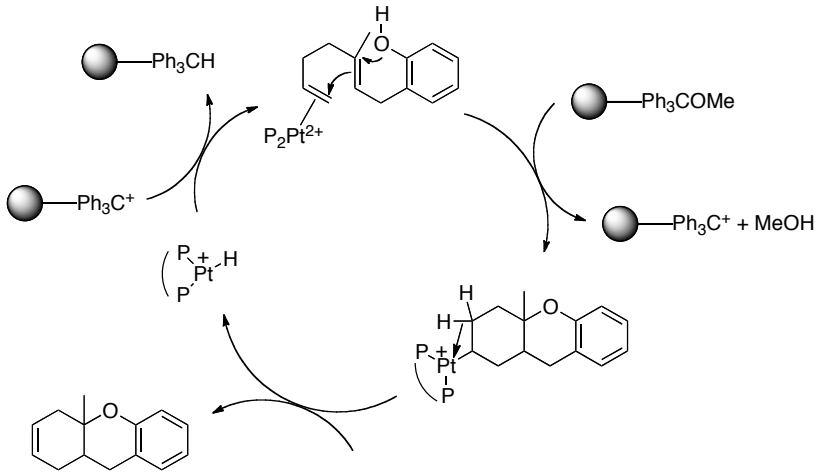


100 **101**

Scheme 28

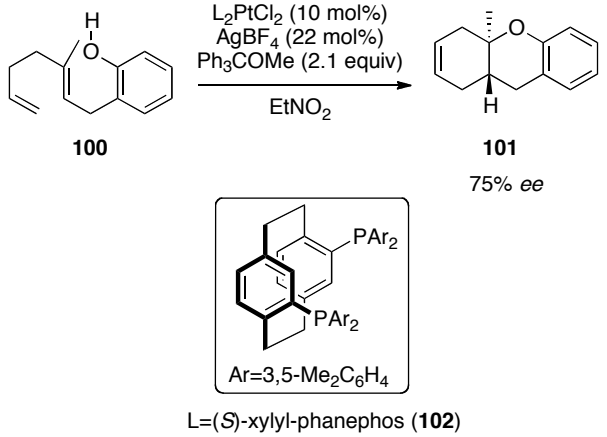
The proposed catalytic cycle is shown in Scheme 29. Coordination and activation of the less substituted C=C double bond by P_2Pt^{2+} initiated the cascade cyclization. A turnover limiting *β*-hydride elimination took place to generate the product and a P_2Pt-H cation, which reacted with trityl cation to form triphenylmethane, regenerating the dicationic Pt species.

30 Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc*. **2007**, *129*, 11880−11881.



Scheme 29. Proposed Catalytic Cycle for Trityl Cation-Mediated Oxidative Cyclization

A wide variety of chiral diphosphine ligands were tested to realize the asymmetric conversion of **100** to **101** (Scheme 30). The best ligand was (*S*)-xylyl-phanephos (**102**), yielding **101** in 75% *ee*.[31]

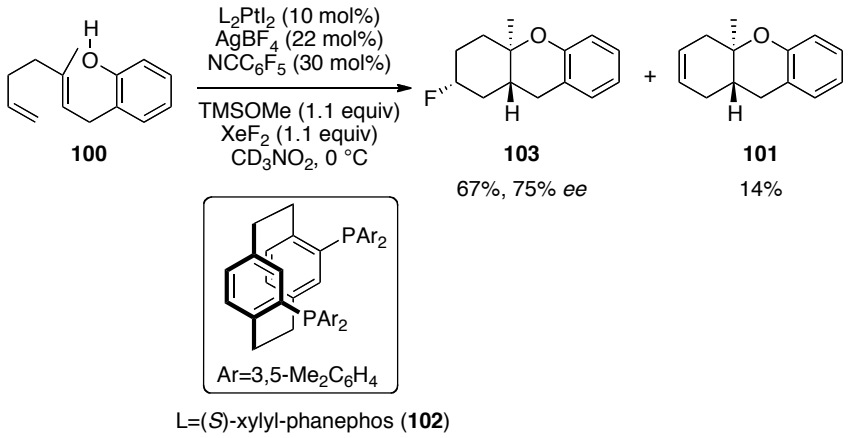


Scheme 30

The *β*-hydride elimination of the intermediate P_2Pt-cycloalkyl cation could be intercepted by a Pt-C fluorination reaction to generate C3-

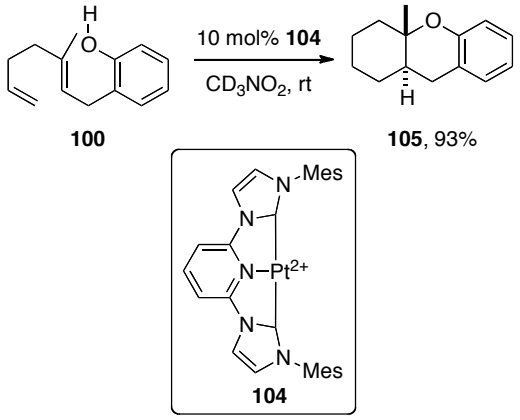
31 Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011−6014.

fluorinated product in good yield and moderate enantioselectivity (Scheme 31).[32]



Scheme 31

The group of Gagné also reported a Pt-catalyzed diastereoselective cascade cyclization enabled by a tridentate NHC containing pincer ligand (Scheme 32).[33] The complex **104** was not only sufficiently electrophilic to initiate the cation olefin cyclization but also electron rich enough to under rapid protodemetalation. Thus, **100** was completely converted to the cyclization/protonolysis product **105** using 10 mol% of **104** after 3 h at room temperature.



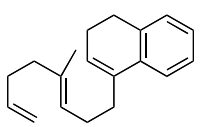
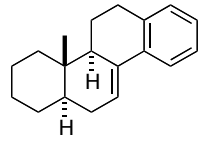
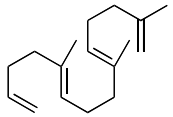
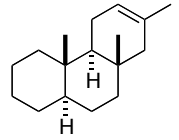
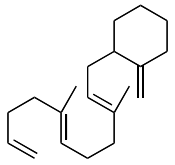
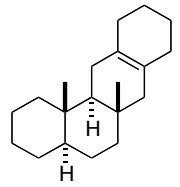
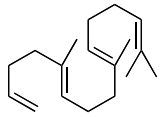
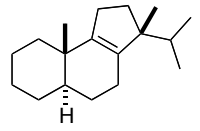
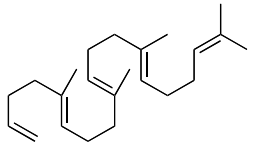
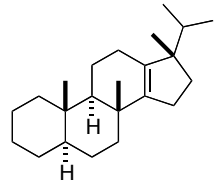
Scheme 32

32 Cochrane, N. A.; Nguyen, H.; Gagné, M. R. *J. Am. Chem. Soc*. **2013**, *135*, 628−631.

33 Geier, M. J.; Gagné, M. R. *J. Am. Chem. Soc*. **2014**, *136*, 3032−3035.

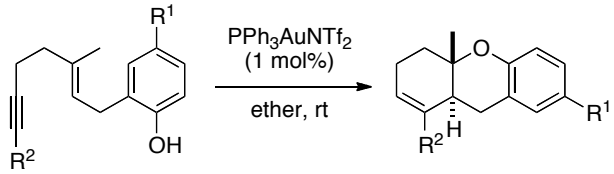
Bi-, tri- and tetracyclized products could be obtained as single diastereomers in moderated yields (Table 3). It is noteworthy that these hydrocarbon containing substrates must overcome the lack of H-bond assistance in the terminating alkene, often leading to slow reactions and incomplete cyclization using other methods.

Table 3. Selected Examples of Pt Catalyzed Polyene Cyclization

Entry	Substrate	Product	Solvent	Isolated Yield
1			CD_3NO_2	70%
2			CD_3NO_2	61%
3			CH_2Cl_2	59%
4			CH_2Cl_2	39%
5			CH_2Cl_2	44%

In 2009, the Michelet group reported a gold-catalyzed phenoxycyclization of 1,5-enynes.[34] Under mild conditions with PPh_3AuNTf_2 as the catalyst, 1,5-enynes **106** were converted to tricyclic functionalized heterocycles **107** in good to excellent yields as single diastereomers (Scheme 33).

34 Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett*. **2009**, *11*, 2888−2891.



106

106a: R^1=H, R^2=Me
106b: R^1=Cl, R^2=Me
106c: R^1=Me, R^2=Me
106d: R^1=Br, R^2=Me
106e: R^1=OMe, R^2=H
106f: R^1=OMe, R^2=Ph

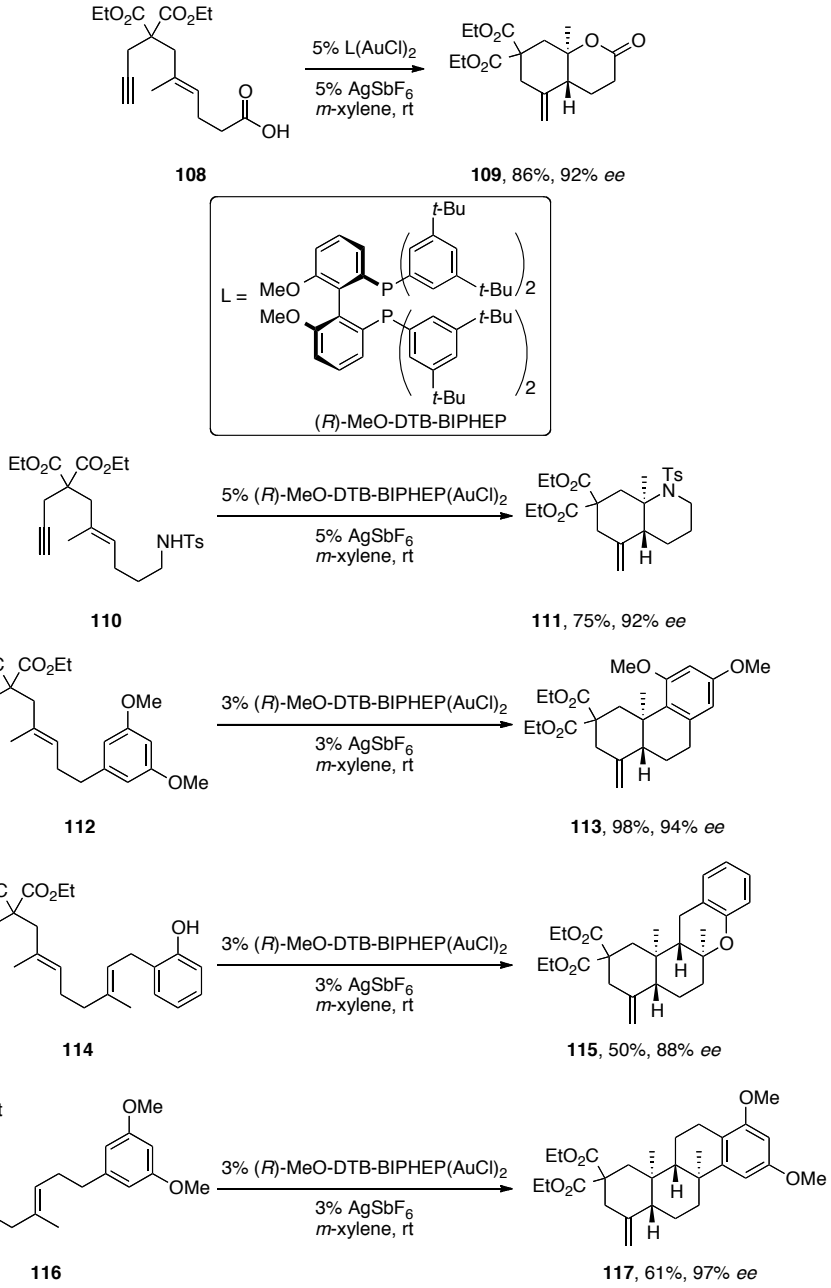
107

107a: 76%
107b: 80%
107c: 80%
107d: 89%
107e: 96%
107f: 83%

Scheme 33. 1,5-Enyne Cyclizations Catalyzed by PPh_3AuNTf_2

In 2010, the Toste group reported a highly enantioselective polyene cyclization catalyzed by a chiral gold(I) complex.[35] (*R*)-MeO-DTB-BIPHEP$(AuCl)_2$ was used as precatalyst, after Cl abstraction by $AgSbF_6$, to activate the alkynyl group in the substrate to initiate the polycyclization in *m*-xylene at room temperature. Single diastereomers and excellent enantioselectivities were obtained when acid, amide, phenol, and electron rich aromatic rings were used as the terminal nucleophile (Scheme 34).

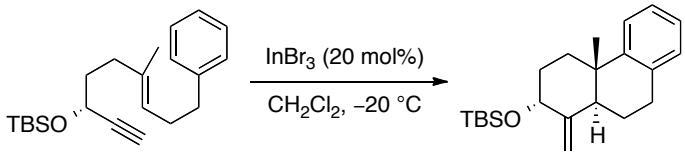
35 Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc*. **2010**, *132*, 8276−8277.


EtO2C CO2Et
5% L(AuCl)2
5% AgSbF6
m-xylene, rt
O
OH
108
109, 86%, 92% ee
t-Bu
L = MeO
MeO
P
t-Bu
2
(R)-MeO-DTB-BIPHEP
NHTs
110
111, 75%, 92% ee
Ts
N
3% (R)-MeO-DTB-BIPHEP(AuCl)2
3% AgSbF6
OMe
112
113, 98%, 94% ee
OH
114
115, 50%, 88% ee
116
117, 61%, 97% ee

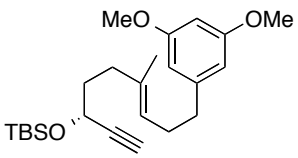
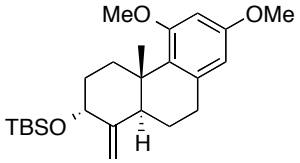
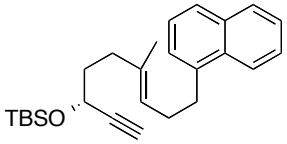
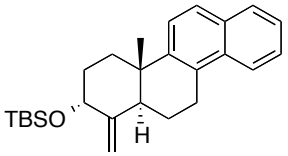
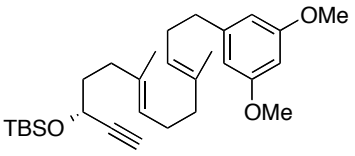
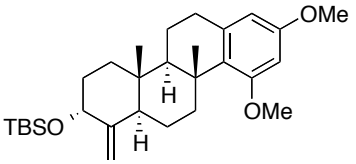
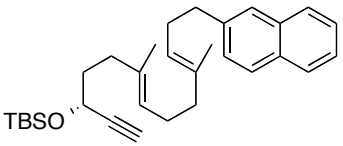
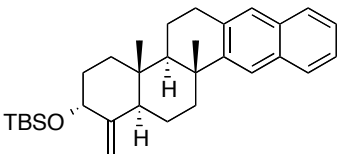
Scheme 34

In 2011, Corey and co-workers reported an indium(III)-catalyzed cationic cascade cyclization.[36] Thus, substrate **118** was stereoselectively converted into **119** in 78% yield using 20 mol% $InBr_3$ in CH_2Cl_2 at −20 °C (Table 4).

Table 4. $InBr_3$-Catalyzed Polycyclization in CH_2Cl_2 at −20 °C



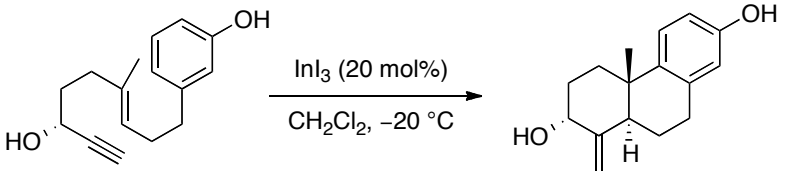
118 **119**, 78%

Entry	Substrate	Product	Yield
1	 **120**	 **121**	90%
2	 **122**	 **123**	88%
3	 **122**	 **123**	82%
4	 **124**	 **125**	60%

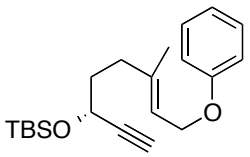
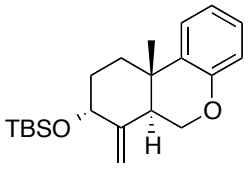
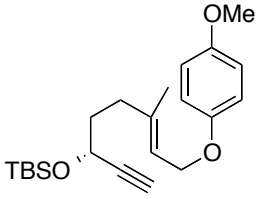
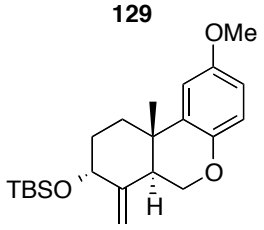
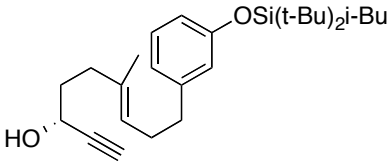
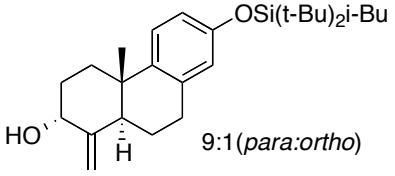
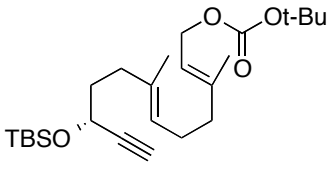
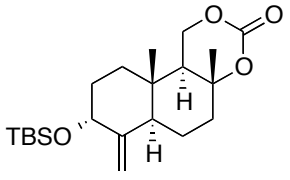
36 Surendra, K.; Qiu, W.; Corey, E. J. *J. Am. Chem. Soc*. **2011**, *133*, 9724−9726.

The more soluble InI_3 also converted polyenynes to the corresponding polycycles (Table 5). Phenolic hydroxyl substituent, ester function and skeletal ether oxygens did not interfere with the polycyclization process.

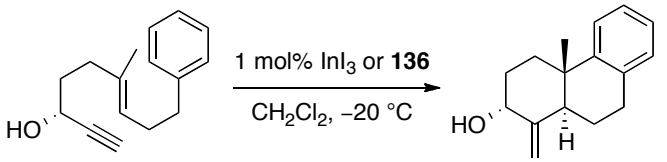
Table 5. InI_3-Catalyzed Polycyclization in CH_2Cl_2 at −20 °C



126 **127**
95%, 1:1(*para:ortho*)

Entry	Substrate	Product	Yield
1	 **128**	 **129**	75%
2	 **130**	 **131**	84%
3	 **132**	 9:1(*para:ortho*) **133**	90%
4	 **134**	 **135**	78%

A more reactive indium catalyst **136** was later developed by treatment of InI_3 with AgBARF in dry CH_2Cl_2 at 0 °C (Scheme 35).[37]



137 **138**

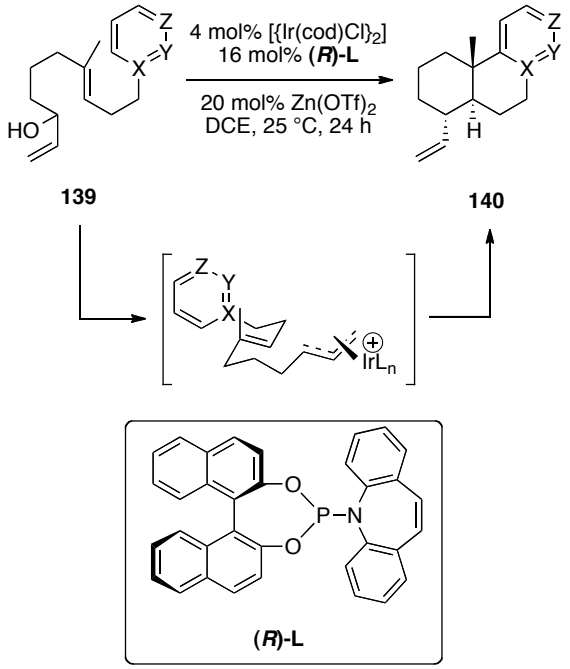
yield with InI_3: 5±2%
yield with **136**: 87%

136: $InI_2^+B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4^-$

Scheme 35. Relative Reactivities of InI_3 and $InI_2^+BARF^-$ in the Cyclization of 137 to 138

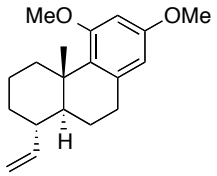
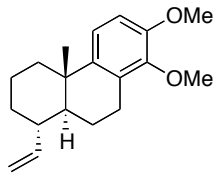
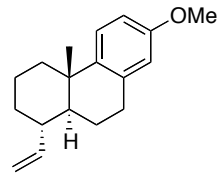
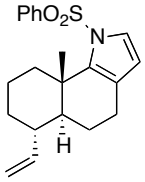
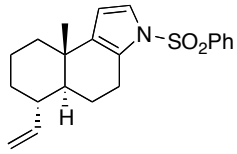
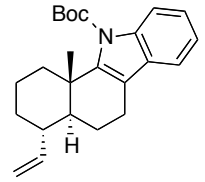
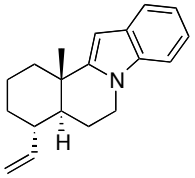
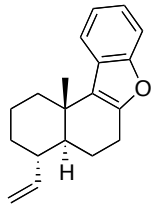
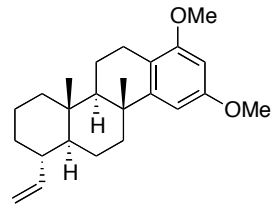
In 2012, Carreira and co-workers reported a highly enantioselective polycyclization enabled by iridium catalysis, which allowed to use unactivated, branched racemic allylic alcohols were used as initiators in enantioselective polycyclizations for the first time (Scheme 36).[38] With $Zn(OTf)_2$ as the promoter, allylic alcohols **139** with different terminal aromatic rings gave the corresponding bicyclized products **140** in good yields and excellent enantioselectivities (Table 6).

37 Surendra, K.; Corey, E. J. *J. Am. Chem. Soc*. **2014**, *136*, 10918−10920.
38 Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc*. **2012**, *134*, 20276−20278.



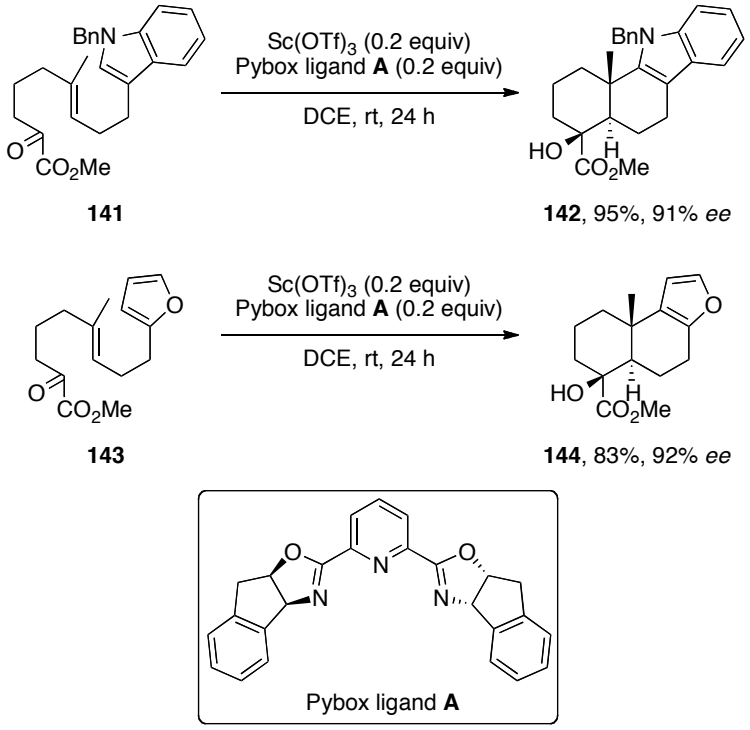
Scheme 36. Ir-Catalyzed Enantioselective Cyclization

Table 6. Scope of the Ir-Catalyzed Polyene Cyclization

		
140a: 90%, >99.5% *ee*	**140b**: 71%, >99.5% *ee*	**140c**: 71%, para/ortho=2:1, >99.5% *ee*
		
140d: 93%, >99.5% *ee*	**140e**: 90%, >99.5% *ee*	**140f**: 86%, >99.5% *ee*
		
140g: 71%, 99% *ee*	**140h**: 89%, 99.5% *ee*	**140i**: 43%, >99.5% *ee*

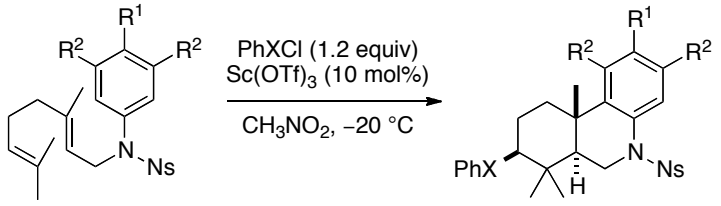
The group of Loh reported an enantioselective polyene cyclization catalyzed by $Sc(OTf)_3$. [39] This efficient catalytic enantioselective cyclization was enabled by the use of 0.2 equiv of $Sc(OTf)_3$ and 0.2 equiv of Pybox ligand **A** with 1,2-dichloroethane as solvent. Under these conditions, substrate **141** and **142** could be converted to the corresponding polycycles in good yields and excellent enantiomeric excesses (Scheme 37).

39 Zhao, Y.-J.; Li, B.; Tan, L. S.; Shen, Z.-L.; Loh, T.-P. *J. Am. Chem. Soc*. **2010**, *132*, 10242−10244.



Scheme 37

Another $Sc(OTf)_3$ catalyzed polyene cyclization was reported in 2013 by the group of Shaw.[40] In this case, 10 mol% of $Sc(OTf)_3$ was used to promote the bicyclization of geranylated anilines in CH_3NO_2 at −20 °C (Scheme 38). This method allowed the installation of PhS- or PhSe-group to the resulting polycycles.



145 **146**

146a: R^1=H, R^2=OMe, X=S, 85%
146a': R^1=H, R^2=OMe, X=Se, 84%
146b: R^1=R^2=OMe, X=S, 92%
146b': R^1=R^2=OMe, X=S, 94%

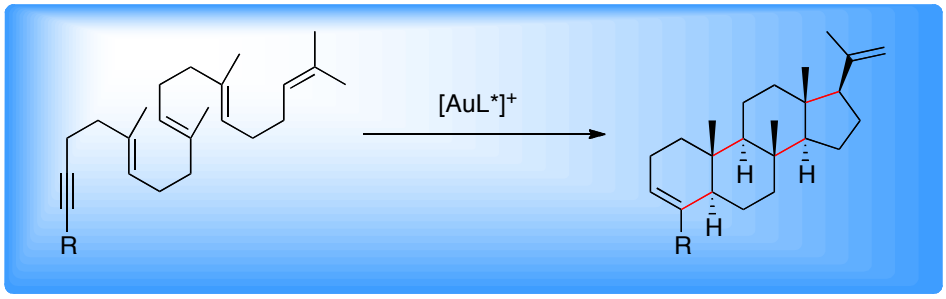
Scheme 38. Bicyclization Reactions of Geranyl Anilines

40 Moore, J. T.; Soldi, C.; Fettinger, J. C.; Shaw, J. T. *Chem. Sci*. **2013**, *4*, 292−296.

General Objectives

Despite some precedents, the potential of gold(I)-catalyzed polycyclization reactions of polyenynes to construct complex molecules has not been fully released. Especially, steroid-like polycyclic compounds have never been synthesized by gold catalysis.

We proposed that selective activation of an alkyne by gold(I) catalyst could be an initiator for cationic polycyclization. By careful design of the substrates, steroid-like products could be obtained. Asymmetric methods could then be employed to furnish enantioenriched polycyclic products (Scheme 39).



Scheme 39. Preparation of Polycyclic Compound from Polyenyne

Chapter 1. Gold(I)-Catalyzed Polycyclizations of 1,5-Enynes: Scope and Limitations

Background

Gold(I)-catalyzed cycloisomerizations of 1,n-enynes, as well as the reactions of these substrates with many nucleophiles, allow the construction of complex carbo- and heterocyclic compounds by the selective activation of the alkyne in the presence of many other functional groups.[41] These transformations have been used as the key steps in the total synthesis of diverse natural products.[42]

Our group has been contributing to the development of gold(I)-catalyzed reactions for the construction of complex molecules and applying these methods to the total synthesis of natural products.[43] Although there are

41 Selected reviews: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal*. **2006**, *348*, 2271−2296. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed*. **2007**, *46*, 3410−3449. (c) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180−3211. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev*. **2008**, *108*, 3326−3350. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev*. **2008**, *108*, 3351−3378. (f) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed*. **2008**, *47*, 4268−4315. (g) Fürstner, A. *Chem. Soc. Rev*. **2009**, *38*, 3028−3221. (h) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev*. **2011**, *111*, 1954−1993. (i) Krause, N.; Winter, C. *Chem. Rev*. **2011**, *111*, 1994−2009. (j) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res*. **2014**, *47*, 902−912. (k) Fensterbank, L.; Malacria, M. *Acc. Chem. Res*. **2014**, *47*, 953−965. (l) Dorel, R.; Echavarren, A. M. *Chem. Rev*. **2015**, *115*, 9028−9072.

42 Selected reviews: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev*. **2008**, *37*, 1766−1775. (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev*. **2012**, *41*, 2448−2462. (c) Fürstner, A. *Acc. Chem. Res*. **2014**, *47*, 925−938. (d) Zhang, Y.; Luo, T.; Yang, Z. *Nat. Prod. Rep*. **2014**, *31*, 489−503.

43 Work towards the synthesis of natural products by using gold catalysis from our group: (a) Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun*. **2009**, 7327−7329. (b) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2010**, *49*, 3517−3519. (c) Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2013**, *52*, 6396−6399. (d) Carreras, J.; Livendahl, M.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2014**, *53*, 4896−4899. (e) Homs, A.; Muratore, M. E.; Echavarren, A. M. *Org. Lett*. **2015**, *17*, 461−463. (f) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett*. **2016**, *18*, 1614−1617. (g) Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc*. **2016**, *138*, 3671−3674. (h) Carreras, J.; Kirillova, M. S.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2016**, *55*, 7121−7125. (i) Dorel, R.; Echavarren, A. M. *J. Org. Chem*. **2016**, *81*, 8444−8454.

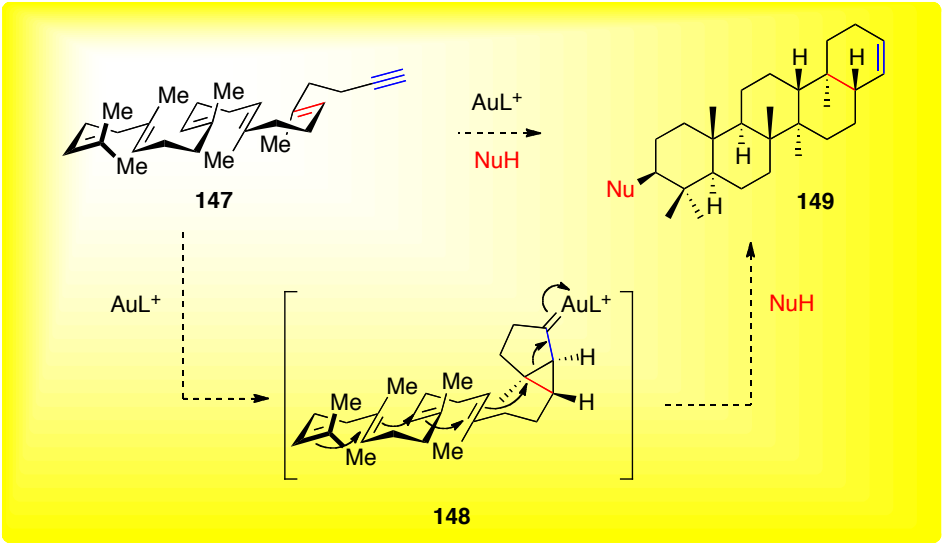
some precedents[44] on gold catalyzed polycyclizations, the scope and limitations of gold catalysis in this context have not been well defined. Moreover, the methods that have been developed by other groups usually require substrates with a terminal nucleophile such as acid, alcohol, amide, phenol, or aromatic rings. The use of an alkene as the terminal nucleophile, which could allow the formation of steroid-like product, had never been achieved.

44 (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed*. **2008**, *47*, 5030−5033. (b) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett*. **2009**, *11*, 2888−2891. (c) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc*. **2010**, *132*, 8276−8277. (d) Pradal, A.; Chen, Q.; Faudot dit Bel, P.; Toullec, P. Y.; Michelet, V. *Synlett* **2012**, *23*, 74−79.

Objectives

As is mentioned above, gold(I)-catalyzed polycyclization that uses substrates with an alkene as the terminal nucleophile has not been reported. These substrates would give polycyclic products with a steroid-like skeleton.

Thus, we proposed that polyenyne **147**, which could be prepared from squalene, could be activated with a cationic gold(I) catalyst to afford intermediate **148** which could undergo a polyene cyclization, leading to a pentacyclic triterpenoid-like compound **149** (Scheme 40).



Scheme 40. Proposed Gold(I)-Catalyzed Polycyclization

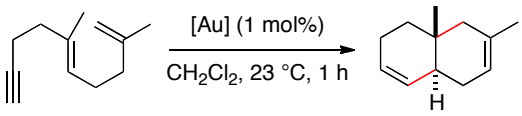
Results and Discussions

Reaction Optimization

First, we examined the cyclization of *(E)*-2,6-dimethyldeca-1,5-dien-9-yne (**150**) with gold(I) catalysts **C1**-**6** bearing electronically different bulky groups (Table 7). In all cases, *trans*-fused hexahydronaphthalene **151** was cleanly obtained as the major product after 1 h by using just 1 mol% catalyst. As we have observed before in other contexts, the best yields were obtained with cationic gold(I) complexes bearing very bulky biphenylphosphine ligands.[45] In this particular instance, cationic dicyclohexylphosphinobiphenyl gold(I) complex **C3** outperforms Johnphos, *t*-BuXphos and Xphos complexes **C1**, **C2**, and **C4** (Table 7, entries 1-4).

45 (a) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res*. **2014**, *47*, 902−912. (b) Ranieri, B.; Escofet, I.; Echavarren, A. M. *Org. Biomol. Chem*. **2015**, *13*, 7103−7118. (c) Miller, R.; Carreras, J.; Muratore, M. E.; Gaydou, M.; Camponovo, F.; Echavarren, A. M. *J. Org. Chem*. **2016**, *81*, 1839−1849.

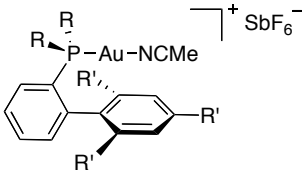
Table 7. Gold(I)-Catalyzed Cyclization of dienyne 150[a]



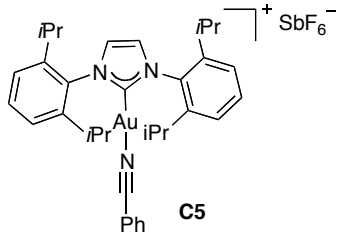
150 **151**

Entry	Catalyst	Yield (%)[b]
1	**C1**	84
2	**C2**	45
3	**C3**	90
4	**C4**	41
5	**C5**	61
6	**C6**	45

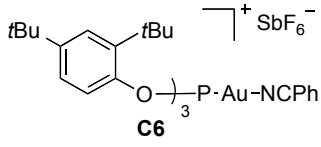
[a] Reactions carried out with **150** (0.3 mmol), catalyst (3 μmol) in CH_2Cl_2 (3 mL) at 23 °C for 1h.
[b] isolated yields.



C1: R = *t*-Bu, R' = H
C2: R = *t*-Bu, R' = *i*-Pr
C3: R = Cy, R' = H
C4: R = Cy, R' = *i*-Pr



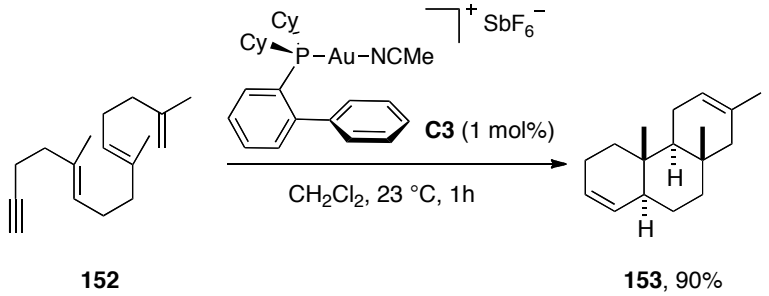
C5



C6

Study of the Reaction Scope

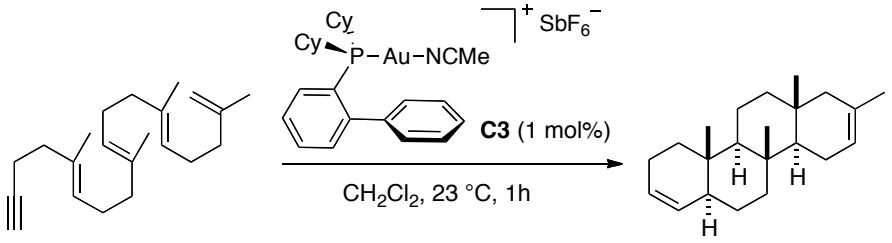
With the optimized conditions in hand, we decided to explore the generality and potential limitations of this cyclization by extending the polyenyne chain. Thus, trienyne **152** was treated with the optimized conditions and the tricyclic product **153** was obtained as a single diastereomer in very good yield (Scheme 41).



152 **153**, 90%

Scheme 41. Gold(I)-Catalyzed Cyclization of Trienyne 152

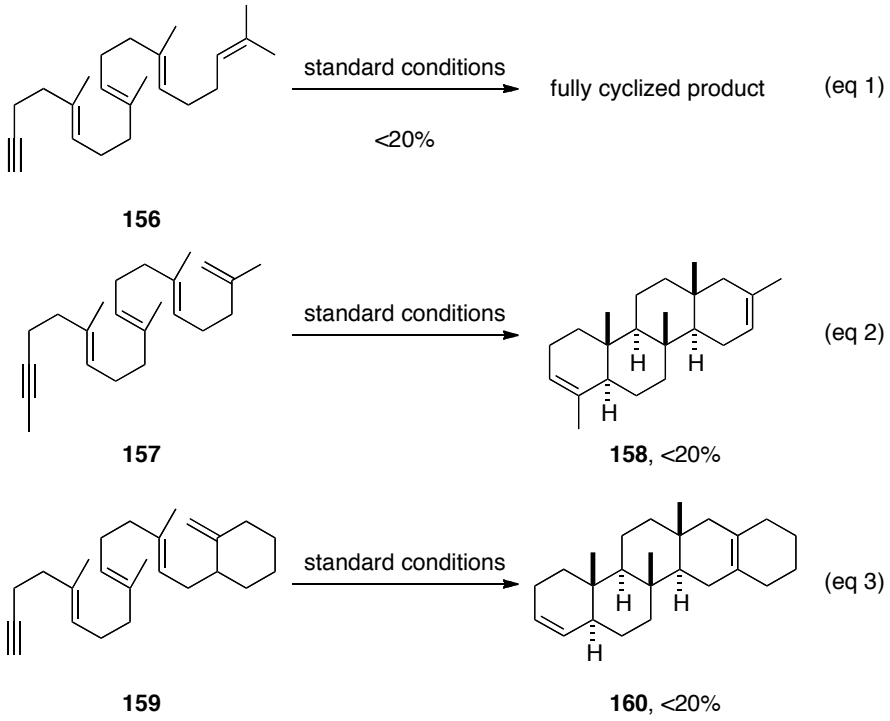
Tetraenyne **154** was submitted to the identical conditions as **152** and tetracyclic product **155** was obtained as a single diastereomer (Scheme 42). In this case, there is a significant decrease in yield (59%). However, considering that four C−C bonds are formed in a single step with a low catalyst loading, this transfomation is quite remarkable.



154 **155**, 59%

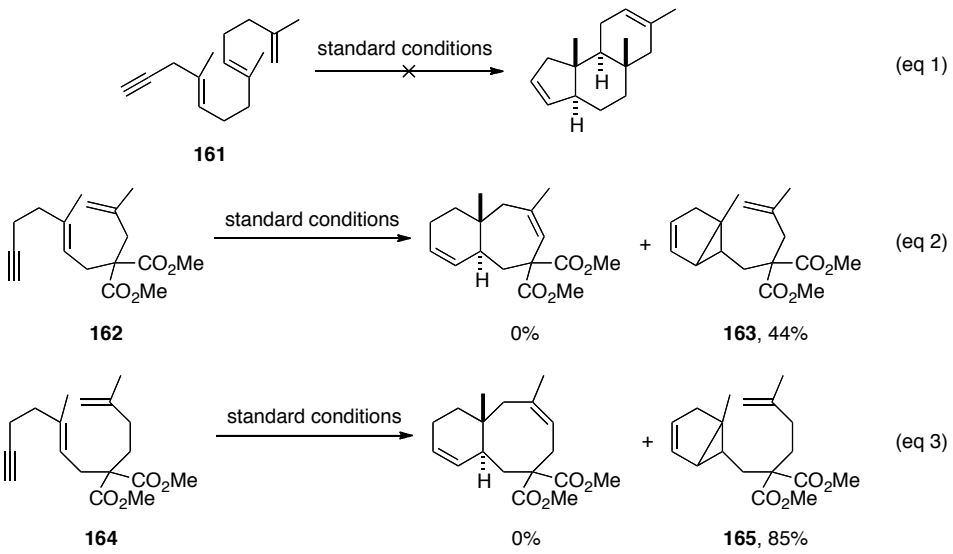
Scheme 42. Gold(I)-Catalyzed Cyclization of Tetraenyne 154

Tetraenyne **156** was also treated under the standard conditions and the anticipated fully cyclized product was formed in poor yield (<20% determined by NMR) and could not be isolated from other products (Scheme 43, eq 1). So, the structure of the product could not be fully assigned. Rising or reducing the temperature did not increase the yield. The same applies for substrates **157** (Scheme 43, eq 2) and **159** (Scheme 43, eq 3).



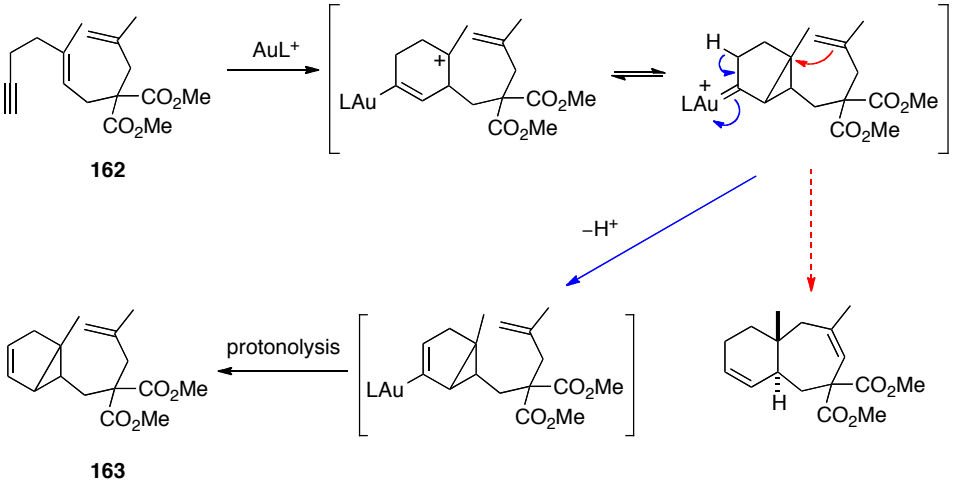
Scheme 43. Gold(I)-Catalyzed Cyclization of Tetraenyne 156, 157 and 159

The formation of five, seven and eight membered rings was also tested. 1,4-enyne **161** was treated under the standard conditions but no fused prodcut was obtained (Scheme 44, eq 1). Compounds **162** and **164** were used to form the 6+7 and 6+8 fused products, respectively. However, only partially cyclized compound **163** and **165** were obtained (Scheme 44, eq 2 and eq 3).



Scheme 44. Gold(I)-Catalyzed Cyclization of Tetraenyne 161, 162 and 164

The formation of **163** and **165** could be explained by the inability of the terminal alkene to attack the intermediate and proton elimination and protonolysis take place, leading to the formation of the undesired product (Scheme 45).

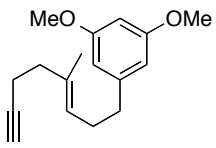
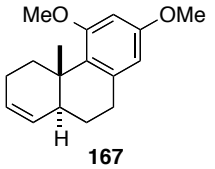
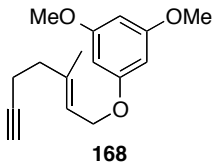
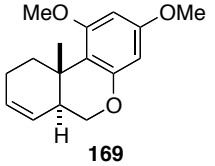
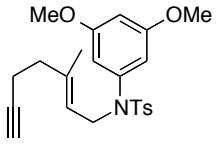
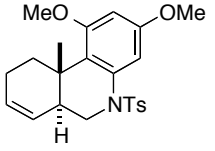
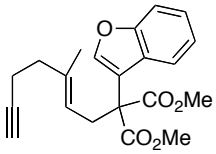
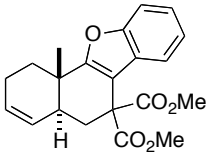
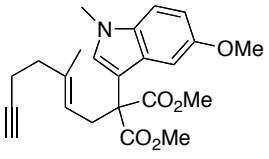
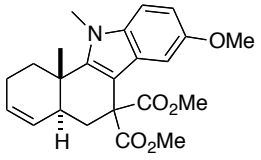


Scheme 45. Proposed Mechanism for the Formation of 163

Aryl substituted 1,5-enynes were then examined with the same gold(I) catalyst. The reaction of substrates **166**, **168**, **170**, **172**, and **174** bearing electron-rich aromatic and heteroaromatic rings as cyclization terminators proceeded in good yields in most cases to give bicyclized products as

single diastereomers (Table 8). The reaction conditions are identical to that used before except that 3 mol% of catalyst is needed to achieved complete conversion. The *trans*-relative configuration of indole derivative **175** was confirmed by X-ray diffraction (Figure 4).

Table 8. Gold(I)-Catalyzed Cyclization of Aryl or Heteroaryl 1,5-enynes[a]

Entry	Substrate	product	yield (%)[b]
1	 **166**	 **167**	95
2	 **168**	 **169**	54
3	 **170**	 **171**	79
4	 **172**	 **173**	80
5	 **174**	 **175**	95

[a] Reactions carried out with catalyst **C3** (3 mol%) in CH_2Cl_2 (0.1 M) at 23 °C for 1 h.
[b] Isolated yields.

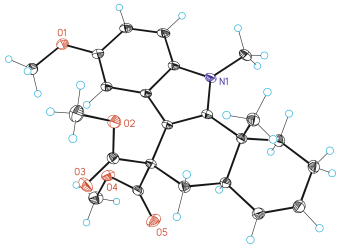
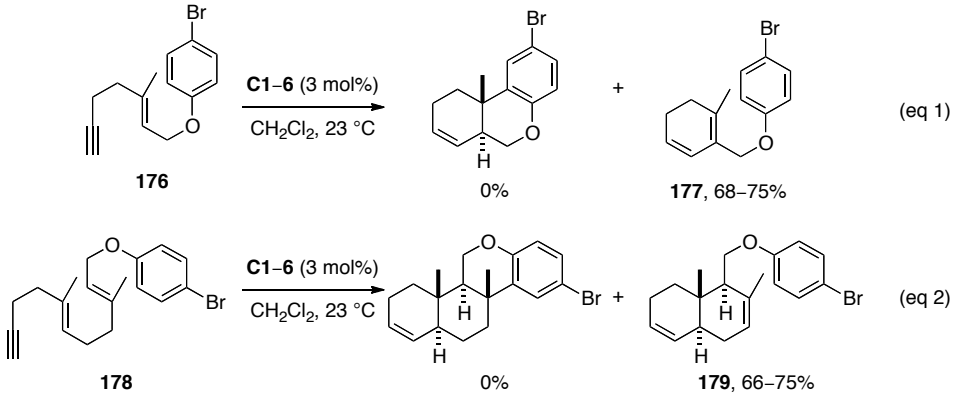


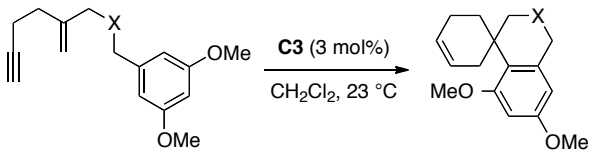
Figure 4. ORTEP plot (50% thermal ellipsoids) of the crystal structure of 175

When substrates bearing electron-deficient aromatic rings such as **176** and **178** were employed, no completely cyclized products were obtained. Instead, partially cyclized compounds **177** and **179** were isolated (Scheme 46). Switching to other gold(I) complexes did not give the desired products.



Scheme 46. Gold(I)-Catalyzed Cyclization of Enyne 176 and 178

Spirocyclic compounds can also be obtained using the same strategy. 1,5-Enynes **180** and **181** were exposed to 3 mol% of catalyst **C3** in CH_2Cl_2 at 23 °C for 1 h, giving rise to the formation of the spirocyclic derivatives **182** and **183** in good yields (Scheme 47). The structure of product **183** was also confirmed by X-ray diffraction (Figure 5).



Scheme 47. Gold(I)-Catalyzed Cyclization of Enyne 180 and 181

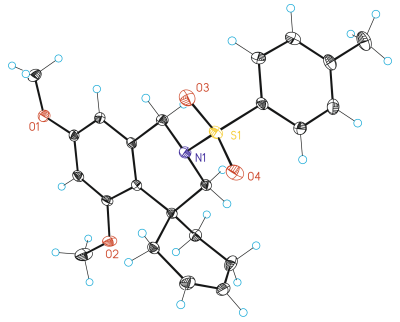
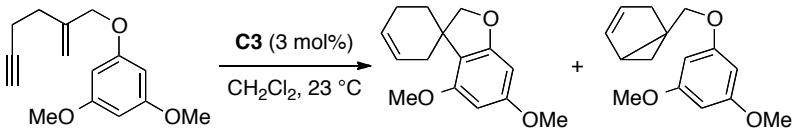


Figure 5. ORTEP plot (50% thermal ellipsoids) of the crystal structure of 183

However, when substrate **184** was employed to form the spirobenzofuran derivative, no desired product was obtained (Scheme 48). The main product was the cyclopropane **185** which could be formed through a similar pathway as **163** (see Scheme 45).



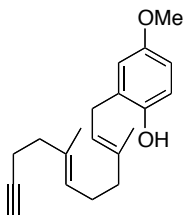
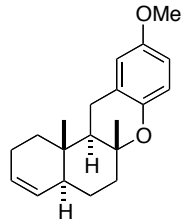
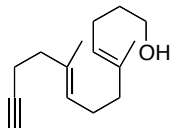
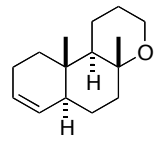
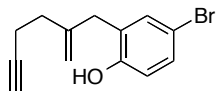
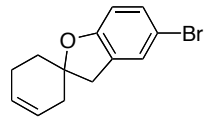
184 0% **185**, 78%

Scheme 48. Gold(I)-Catalyzed Cyclization of Enyne 184

The polycyclization of 1,5-enynes with hydroxyl groups as internal terminators was also studied. As expected considering the precedents,[46] substrate **186** gave tricyclized product **187** as a single diastereomer in excellent yield (Table 9, entry 1). The cyclization of alcohol **188** also proceeded smoothly to yield the corresponding tricyclic product (Table 9, entry 2). Spirobenzofuran **191** was obtained from **190**, which could be applied for the synthesis of analogues of the natural product filifolinol[47] (Table 9, entry 3).

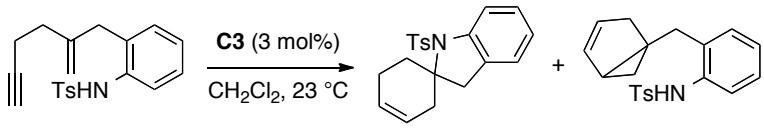
46 Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett*. **2009**, *11*, 2888−2891.
47 Torres, R.; Villattoel, L.; Urzua, A.; Monache, F. D.; Monache, G. D.; Gacs-Baitz, E. *Phytochemistry* **1994**, *36*, 249−250.

Table 9. Gold(I)-Catalyzed Cyclization of Hydroxyl 1,5-enynes[a]

Entry	Substrate	Product	yield (%)[b]
1	 **186**	 **187**	89
2[c]	 **188**	 **189**	75
3	 **190**	 **191**	96

[a] Reactions carried out with catalyst **C3** (3 mol%) in CH_2Cl_2 (0.1 M) at 23 °C for 1 h.
[b] Isolated yield.
[c] 1 mol% of **C3** was used.

Since 2-spirobenzofuran derivative **191** can be formed by our method, we then tested the formation of 2-spiroindoline **193** using aniline **192** as the substrate. To our disappointment, only cyclopropane **194** was obtained (Scheme 49).



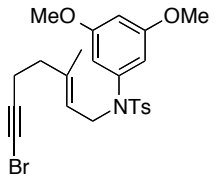
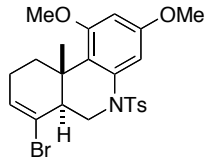
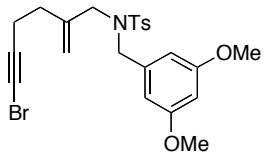
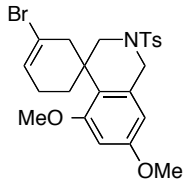
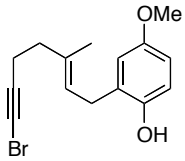
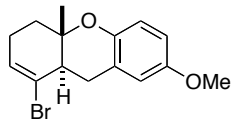
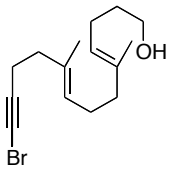
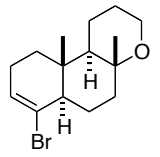
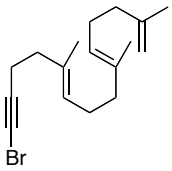
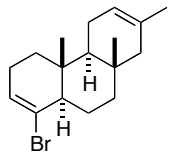
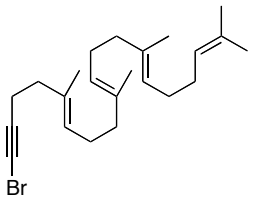
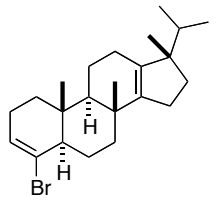
192 **193**, 0% **194**, 84%

Scheme 49. Gold(I)-Catalyzed Cyclization of Enyne 192

1-Substituted 1,5-enynes were also examined as the polycyclization substrates. We first tried 1-bromo-1,5-enyne **195** under the general conditions, which led to cyclized product **196** in 92% yield (Table 10, entry 1). We then tested different 1-bromo-1,5-enynes bearing electron-

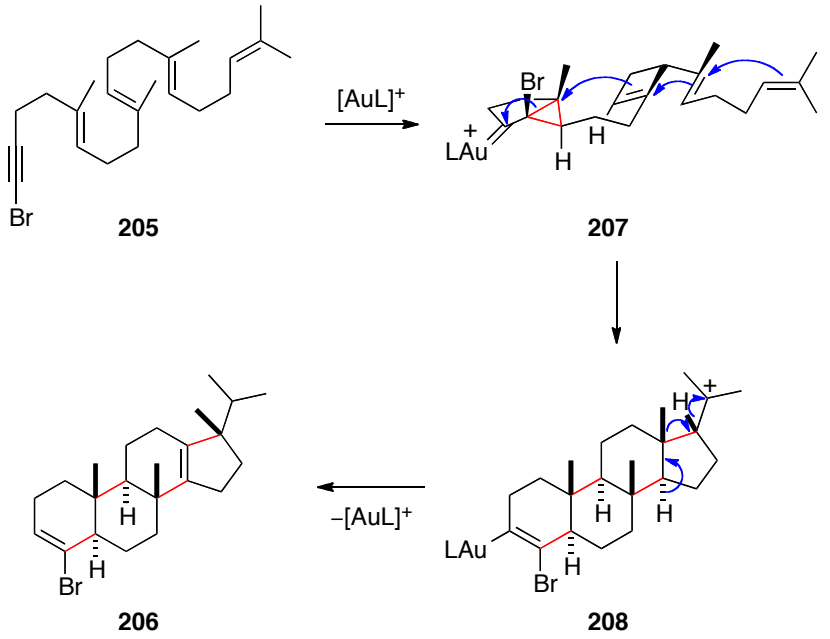
rich aromatic ring, phenol, alcohol, and alkene as internal terminators (Table 10, entry 2-5). In all cases, the polycyclization underwent smoothly without any significant decrease in yield to furnish bromoalkenes which could be further functionalized by metal-catalyzed cross-couplings, carbonylations or by other methods.

Table 10. Gold(I)-Catalyzed Cyclization of 1-bromo-1,5-enynes[a]

Entry	Substrate	Product	yield (%)[b]
1	 **195**	 **196**	92
2	 **197**	 **198**	88
3	 **199**	 **200**	68
4	 **201**	 **202**	78
5	 **203**	 **204**	84
6[c,d]	 **205**	 **206**	51

[a] Reactions carried out with catalyst **C3** (3 mol%) in CH_2Cl_2 (0.1 M) at 23 °C for 1 h.
[b] Isolated yield.
[c] 1 mol% of **C3** was used.
[d] Reaction at 0 °C.

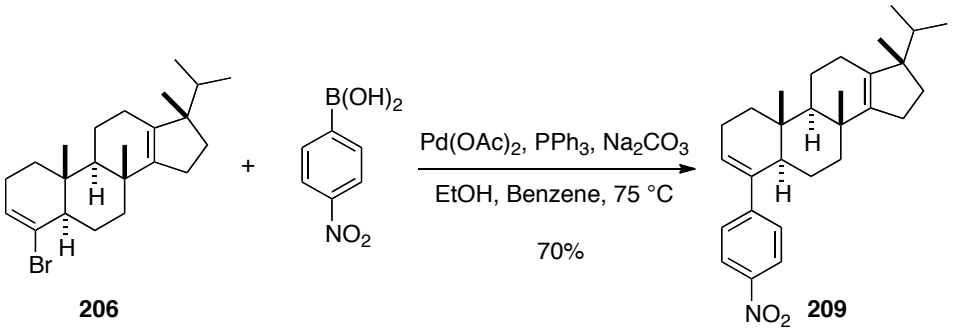
It is noteworthy that 1-bromo-1,5-tetraenyne **205** cyclized at 0 °C to give a 6/6/6/5 ring skeleton in moderate yield (Table 10, entry 6). Presumably, the cyclization of **205** to give **206** proceeds by the initial formation of gold(I)-carbene intermediate **207**, which triggers a cascade process to form secondary carbocation **208** (Scheme 50). The final product **206** is then formed by Wager-Meerwein 1,2-H and Me migrations,[48] followed by proton elimination and protonolysis of the alkenyl-gold(I) bond.



Scheme 50. Proposed Mechanism for the Formation of 206

Considering that four C-C bonds were formed in a single step, this transformation is remarkable for its low catalyst loading and promising further functionalization. Indeed, Suzuki cross-coupling of **206** with 4-nitrophenylboronic acid proceeded smoothly to give **209** in 70% yield (Scheme 51).

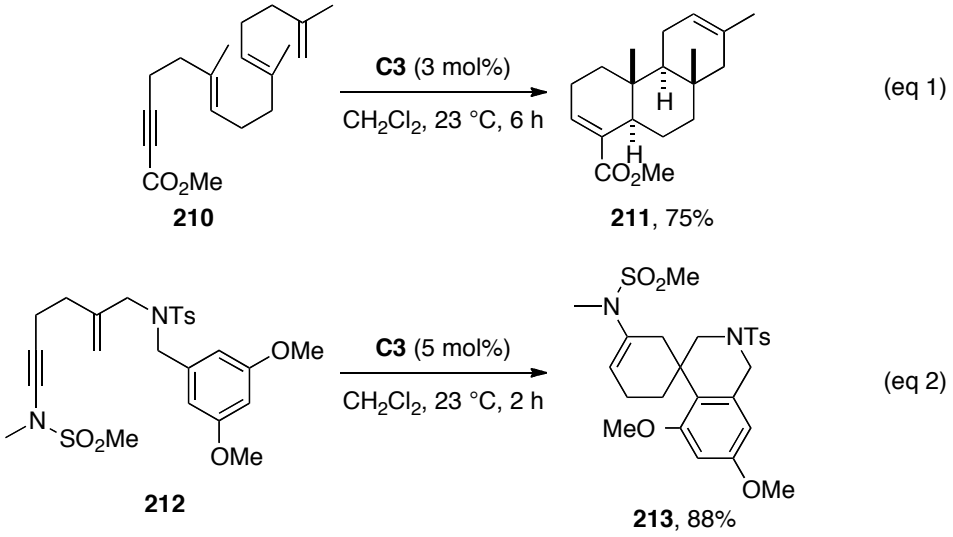
48 (a) Geier, M. J.; Gagné, M. R. *J. Am. Chem. Soc*. **2014**, *136*, 3032−3035. (b) Felix, R. J.; Munro-Leighton, C.; Gagné, M. R. *Acc. Chem. Res*. **2014**, *47*, 2319−2331.



206 **209**

Scheme 51. Formation of 209 by Suzuki Cross-Coupling

1,5-Enynes **210** and **212** with electron-deficient groups at C-1 were then tested for polycyclization. Methyl ester-substituted 1,5-enyne **210** gave polycyclic product **211** in 75% yield under the usual conditions after 6 h (Scheme 52, eq 1). In the case of ynamide **212**, 5 mol% of catalyst **C3** was needed for full conversion to product **213** (Scheme 52, eq 2). 1-Iodo substituted substrates were also tested, but the reactions led to low yields.



210 **211**, 75%

212 **213**, 88%

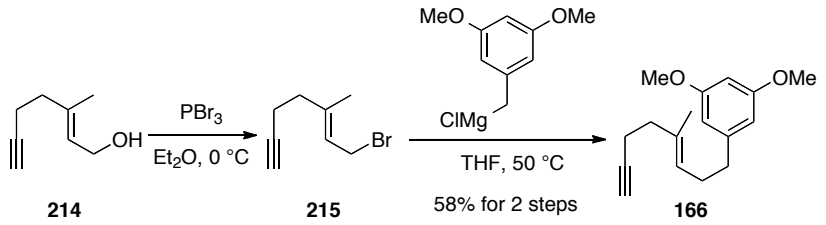
Scheme 52. Gold(I)-Catalyzed Cyclization of Enyne 210 and 212

Conclusions

We have explored the scope of gold(I)-catalyzed polycyclization for 1,5-enynes. Terminal 1,5-enynes bearing electron-rich aromatic rings, phenols, alcohols and alkenes as internal terminators were found to be appropriate substrates for polycyclization. With gold(I) complex **C3** as the catalyst, these substrates furnished the corresponding polyfused and spirocyclic products in moderate to excellent yields. 1-bromo-1,5-enynes were also found to undergo polycyclization reaction smoothly to yield alkenyl bromides, which offers a handle for further functionalization.

Experimental Part

(*E*)-1,3-Dimethoxy-5-(4-methyloct-3-en-7-yn-1-yl)benzene (166)



Phosphorus tribromide (33 μL, 0.35 mmol) was added dropwise to a solution of **214**[49] in Et_2O (7 mL) at 0 °C and the mixture was stirred at this temperature for 30 minutes before 10 mL of water was added. The aqueous layer was extracted with Et_2O (5 mL) and the combined organic layer was washed sequentially with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated to give **215** as colorless oil which was used without further purification.

To **215** was added (3,5-dimethoxybenzyl)magnesium chloride (5.2 mL, 0.2 M in THF, 1.04 mmol) at 0 °C and the mixture was stirred at 50 °C for 5 h before it was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (5 mL) and the combined organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to give **166** (103.2 mg, 58% for two steps) as colorless oil.

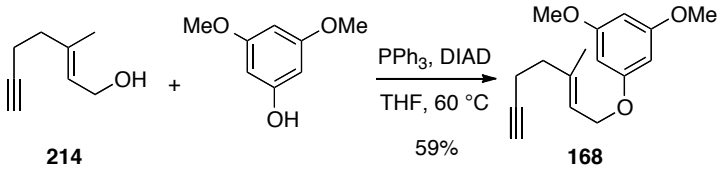
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 2.3 Hz, 2H), 6.33 (t, J = 2.3 Hz, 1H), 5.28 (ddq, J = 8.4, 7.1, 1.3 Hz, 1H), 3.81 (s, 6H), 2.62 (dd, J = 8.9, 6.7 Hz, 2H), 2.39 - 2.27 (m, 4H), 2.27 - 2.20 (m, 2H), 1.98 (t, J = 2.5 Hz, 1H), 1.62(s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.67, 144.7, 134.0, 124.9, 106.6, 97.7, 84.4, 68.4, 55.2, 38.4, 36.3, 29.7, 17.6, 15.8.

49 Surendra, K.; Rajendar, G.; Corey, E. J. *J. Am. Chem. Soc*. **2014**, *136*, 642−645.

HRMS-ESI calculated for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1693; found: 259.1697.

(*E*)-1,3-Dimethoxy-5-((3-methylhept-2-en-6-yn-1-yl)oxy)benzene (168)



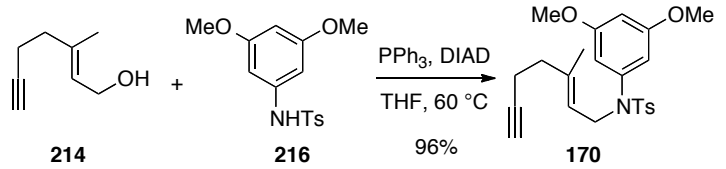
Diisopropyl azodicarboxylate (0.13 mL, 0.66 mmol) was added dropwise to a solution of **214** (54 mg, 0.44 mmol), 3,5-dimethoxyphenol (101 mg, 0.66 mmol) and triphenylphosphine (171 mg, 0.66 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at 60 °C for 3 h. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/CH_2Cl_2 2:1) to give **168** (66.8 mg, 59%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (d, *J* = 2.1 Hz, 2H), 6.12 - 6.10 (m, 1H), 5.57 (ddt, *J* = 7.8, 5.2, 1.3 Hz, 1H), 4.62 - 4.44 (m, 2H), 3.79 (s, 6H), 2.42 - 2.35 (m, 2H), 2.35 - 2.30 (m, 2H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 160.7, 139.1, 120.7, 93.6, 93.0, 83.8, 68.8, 64.7, 55.3, 38.1, 17.2, 16.5.

HRMS-ESI calculated for $C_{16}H_{20}NaO_3$ $[M+Na]^+$: 283.1305; found: 283.1292.

(*E*)-*N*-(3,5-Dimethoxyphenyl)-4-methyl-*N*-(3-methylhept-2-en-6-yn-1-yl)benzenesulfonamide (170)



170 can be prepared by the same method as **168** from **214** and **216**.

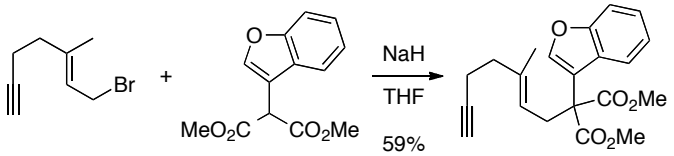
M.p.: 92-94 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.35 - 7.15 (m, 2H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.22 (d, *J* = 2.3 Hz, 2H), 5.19 (ddt, *J* = 6.9, 5.6, 1.3 Hz, 1H), 4.26 - 4.03 (m, 2H), 3.71 (s, 6H), 2.44 (s, 3H), 2.22 - 2.07 (m, 4H), 1.88 (t, *J* = 2.5 Hz, 1H), 1.55 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 143.4, 141.1, 138.4, 135.7, 129.4, 127.8, 120.1, 107.0, 100.0, 83.6, 68.7, 55.4, 48.5, 38.0, 21.5, 17.2, 16.0.

HRMS-ESI calculated for $C_{23}H_{27}NNaO_4S$ $[M+Na]^+$: 436.1553; found: 436.1536.

(*E*)-Dimethyl 2-(benzofuran-3-yl)-2-(3-methylhept-2-en-6-yn-1-yl)malonate (172)



215 **217** **172**

NaH (10.6 mg, 60% dispersion in mineral oil, 0.26 mmol) was added to a solution of **217**[50] (54.6 mg, 0.22 mmol) in THF (3 mL) at 0 °C and the mixture was stirred at this temperature for 30 minutes. A solution of **215** (49.4 mg, 0.26 mmol) in THF (3 mL) was added and the reaction mixture was stirred at 23 °C for 24 h before it was quenched with water (10 mL). The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 7:1) to give **172** (45.9 mg, 59%) as colorless oil.

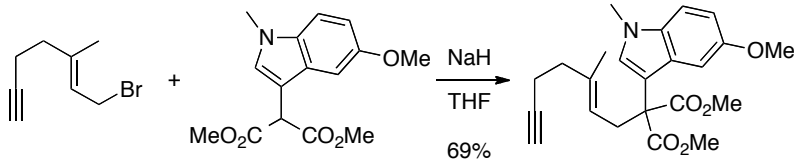
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 - 7.49 (m, 2H), 7.31 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.23 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H), 5.08 (tq, J = 7.4, 1.3 Hz, 1H), 3.76 (s, 6H), 3.17 - 3.12 (m, 2H), 2.23 - 2.11 (m, 4H), 1.93 (t, J = 2.5 Hz, 1H), 1.52 (s, 3H).

50 Liu, Y.; Ma, S. *Org. Lett*. **2012**, *14*, 720−723.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 155.0, 144.2, 137.8, 126.0, 124.3, 122.6, 120.6, 119.0, 116.1, 111.6, 83.9, 68.6, 57.1, 52.8, 38.4, 33.5, 17.5, 15.9.

HRMS-ESI calculated for $C_{21}H_{22}NaO_5$ $[M+Na]^+$: 377.1359; found: 377.1372.

(*E*)-Dimethyl 2-(5-methoxy-1-methyl-1*H*-indol-3-yl)-2-(3-methylhept-2-en-6-yn-1-yl)malonate (174)



215 **218** **172**

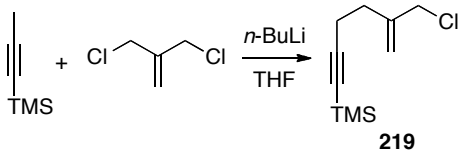
174 can be prepared by the same method as **172** from **215** and **218**[51].

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.20 (dd, J = 8.9, 0.5 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 5.16 (tdd, J = 7.2, 2.7, 1.4 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.74 (s, 6H), 3.17 - 3.14 (m, 2H), 2.24 - 2.14 (m, 4H), 1.94 (t, J = 2.4 Hz, 1H), 1.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 153.9, 136.9, 132.4, 129.1, 126.6, 120.1, 111.8, 110.1, 109.3, 102.3, 84.1, 68.5, 57.8, 55.9, 52.6, 38.5, 34.1, 33.1, 17.7, 16.0.

HRMS-ESI calculated for $C_{23}H_{27}NNaO_5$ $[M+Na]^+$: 420.1781; found: 420.1796.

(5-(Chloromethyl)hex-5-en-1-yn-1-yl)trimethylsilane (219)



219

51 Johansen, M. B.; Kerr, M. A. *Org. Lett*. **2010**, *12*, 4956−4959.

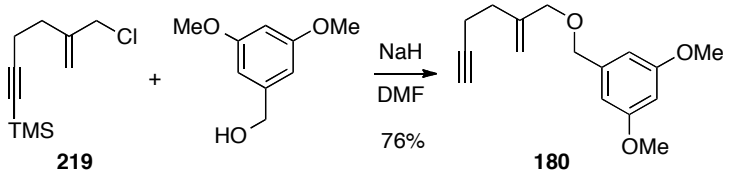
n-BuLi (12 mL, 2.5 M in hexanes, 30 mmol) was added dropwise to a solution of 1-(trimethylsilyl)propyne (4.4 mL, 30 mmol) in THF (300 mL) at -40 °C and the mixture was kept at this temperature for 45 minutes before it was cooled to -78 °C and 3-chloro-2-(chloromethyl)prop-1-ene (3.47 mL, 30 mmol) was added and the reaction mixture was allowed to warmed up to -20 °C during 3 h before it was quenched with saturated aqueous NH_4Cl (300 mL). The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (400 mL) and brine (400 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane) to give **219** (3.20 g, 53%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (d, J = 1.0 Hz, 1H), 5.04 (d, J = 1.1 Hz, 1H), 4.10 (d, J = 1.0 Hz, 2H), 2.43 (m, 4H), 0.16 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 115.5, 106.1, 85.4, 48.0, 32.0, 18.7, 0.1.

HRMS-APCI calculated for $C_{10}H_{18}ClSi$ $[M+H]^+$: 201.0861; found: 201.0858.

1,3-Dimethoxy-5-(((2-methylenehex-5-yn-1-yl)oxy)methyl)benzene (180)



219 **180**

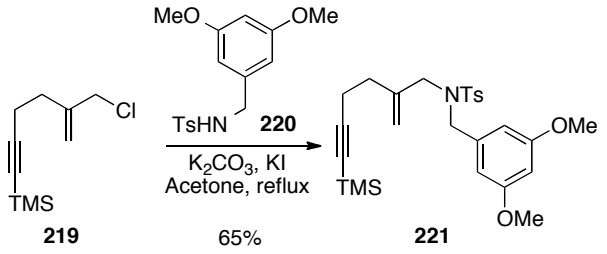
NaH (13.8 mg, 60% dispersion in mineral oil, 0.35 mmol) was added to a solution of 3,5-dimethoxybenzyl alcohol (58.0 mg, 0.35 mmol) in DMF (2 mL) at 0 °C and the mixture was stirred at this temperature for 20 minutes. A solution of **219** (63 mg, 0.31 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at 23 °C for 1.5 h before it was quenched with water (5 mL). The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to give **180** (58.0 mg, 76%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, J = 2.3 Hz, 2H), 6.41 (t, J = 2.3 Hz, 1H), 5.14 (t, J = 1.3 Hz, 1H), 5.04 (d, J = 1.8 Hz, 1H), 4.46 (s, 2H), 4.00 (d, J = 1.2 Hz, 2H), 3.81 (s, 6H), 2.43 - 2.35 (m, 4H), 1.98 (t, J = 2.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 144.1, 140.7, 113.2, 105.3, 99.7, 83.9, 72.9, 71.9, 68.6, 55.3, 32.1, 17.1.

HRMS-ESI calculated for $C_{16}H_{20}NaO_3$ $[M+Na]^+$: 283.1305; found: 283.1311.

***N*-(3,5-Dimethoxybenzyl)-4-methyl-*N*-(2-methylene-6-(trimethylsilyl)hex-5-yn-1-yl)benzenesulfonamide (221)**



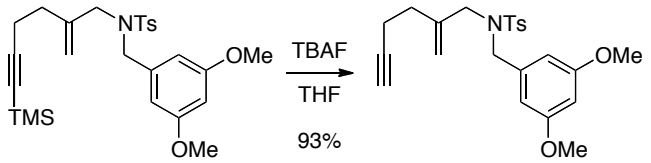
To a solution of **219** (360 mg, 1.79 mmol) and **220** (632 mg, 1.97 mmol) in acetone (20 mL) was added K_2CO_3 (272 mg, 1.97 mmol) and KI (29.7 mg, 0.18 mmol) at 23 °C. The mixture was set to reflux for 24 h before the solvent was evaporated. The residue was taken up in Et_2O (20 mL) and washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 5:1) to give **221** (566 mg, 65%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.35 - 7.30 (m, 2H), 6.34 (t, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 2H), 4.94 (d, J = 1.7 Hz, 1H), 4.87 (d, J = 1.1 Hz, 1H), 4.29 (s, 2H), 3.74 (s, 2H), 3.71 (s, 6H), 2.45 (s, 3H), 2.28 - 2.23 (m, 2H), 2.13 (t, J = 7.3 Hz, 2H), 0.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 143.3, 141.8, 138.2, 137.5, 129.7, 127.2, 115.1, 106.5, 106.4, 99.9, 85.1, 55.3, 52.0, 50.8, 31.9, 21.5, 18.3, 0.1.

HRMS-ESI calculated for $C_{26}H_{35}NNaO_4SSi$ $[M+Na]^+$: 508.1948; found: 508.1948.

***N*-(3,5-Dimethoxybenzyl)-4-methyl-*N*-(2-methylenehex-5-yn-1-yl)benzenesulfona-mide (181)**



221 **181**

Tetrabutylammonium fluoride (1.3 mL, 1.0 M in THF, 1.3 mmol) was added dropwise to a solution of **221** (530 mg, 1.09 mmol) in THF (11 mL) at 0 °C. The reaction mixture was then stirred at 23 °C for 30 minutes before it was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined organic layer was washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 5:1) to give **181** (419 mg, 93%) as a white solid.

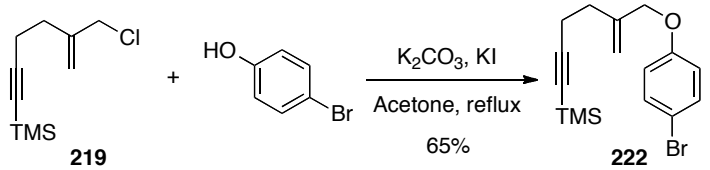
M.p.: 76-77 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.35 - 7.31 (m, 2H), 6.34 (t, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 2H), 4.97 - 4.94 (m, 1H), 4.90 - 4.87 (m, 1H), 4.29 (s, 2H), 3.75 (s, 2H), 3.71 (s, 6H), 2.45 (s, 3H), 2.27 - 2.21 (m, 2H), 2.17 - 2.10 (m, 2H), 1.94 (t, J = 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 143.3, 141.8, 138.2, 137.4, 129.7, 127.2, 115.1, 106.4, 99.9, 83.6, 68.7, 55.3, 52.1, 50.9, 31.7, 21.5, 16.8.

HRMS-ESI calculated for $C_{23}H_{27}NNaO_4S$ $[M+Na]^+$: 436.1553; found: 436.1549.

(5-((4-Bromophenoxy)methyl)hex-5-en-1-yn-1-yl)trimethylsilane (222)



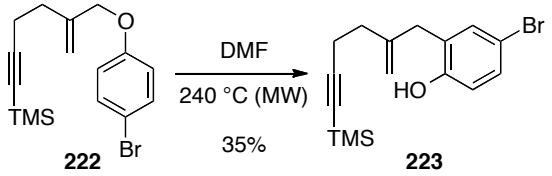
222 can be prepared by the same method as **221** from **219** and 4-bromophenol.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 - 7.37 (m, 2H), 6.85 - 6.81 (m, 2H), 5.20 (dd, J = 1.3, 0.7 Hz, 1H), 5.09 (q, J = 1.1 Hz, 1H), 4.49 (t, J = 1.1 Hz, 2H), 2.49 - 2.43 (m, 2H), 2.42 - 2.36 (m, 2H), 0.16 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.77, 142.80, 132.22, 116.60, 113.60, 113.02, 106.40, 85.33, 70.92, 32.11, 18.87, 0.11.

HRMS-APCI calculated for $C_{16}H_{22}BrOSi$ $[M+H]^+$: 337.0618; found: 337.0615.

4-Bromo-2-(2-methylene-6-(trimethylsilyl)hex-5-yn-1-yl)phenol (223)



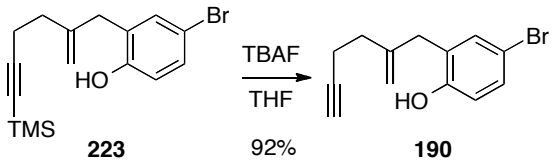
A 5 ml microwave vial was charged with a solution of **222** (200 mg, 0.59 mmol) in DMF (2 mL). The vial was purged with Argon and then fitted with a septa and vial seal. The reaction was then heated to 240 °C under microwave conditions for 2 hours. The reaction mixture was poured into water (10 mL) and extracted with Et_2O. The combined organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to give **223** (70 mg, 35%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 - 7.22 (m, 2H), 6.76 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 5.01 (q, J = 1.2 Hz, 1H), 4.87 (t, J = 1.5 Hz, 1H), 3.39 (s, 2H), 2.50 - 2.43 (m, 2H), 2.29 (m, 2H), 0.18 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 145.4, 133.5, 130.9, 126.9, 118.0, 113.3, 112.7, 106.3, 86.1, 37.5, 34.3, 18.9, 0.1.

HRMS-ESI calculated for $C_{16}H_{20}BrOSi$ $[M-H]^-$: 335.0472; found: 335.0461.

4-Bromo-2-(2-methylenehex-5-yn-1-yl)phenol (190)



223 92% **190**

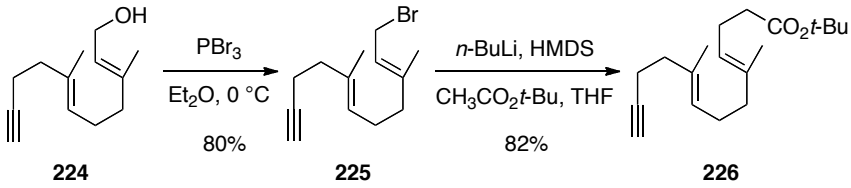
190 can be prepared by the same method as **181** from **223**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 - 7.24 (m, 2H), 6.75 (d, J = 8.4 Hz, 1H), 5.19 (s, 1H), 5.04 (q, J = 1.2 Hz, 1H), 4.92 (q, J = 1.4 Hz, 1H), 3.39 (s, 2H), 2.43 (tdd, J = 7.1, 2.6, 0.8 Hz, 2H), 2.30 (t, J = 7.0 Hz, 2H), 2.05 (t, J = 2.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 145.3, 133.5, 130.9, 126.9, 117.9, 113.3, 112.8, 83.6, 69.3, 37.5, 34.1, 17.2.

HRMS-ESI calculated for $C_{13}H_{12}BrO$ $[M-H]^-$: 263.0077; found: 263.0080.

(4*E*,8*E*)-*tert*-Butyl 5,9-dimethyltrideca-4,8-dien-12-ynoate (226)



225 can be prepared by the same method as **215** from **224**[52].

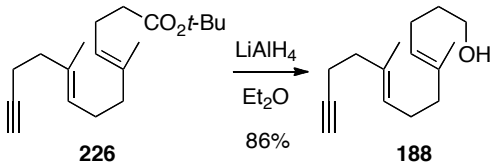
n-BuLi (2.5 mL, 2.5 M in hexanes, 6.3 mmol) was added dropwise to a solution of hexamethyldisilazane (1.37 mL, 6.6 mmol) in THF (15 mL) at -78 °C and the mixture was kept at 0 °C for 30 minutes before it was re-cooled to -78 °C and *tert*-butyl acetate (0.44 mL, 3.3 mmol) was added. After 1 h, a solution of **225** (762 mg, 2.99 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 °C for 30 minutes before it was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to give **226** (711 mg, 82%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (tq, J = 7.1, 1.4 Hz, 1H), 5.12 (ddt, J = 6.9, 5.5, 1.3 Hz, 1H), 2.32 - 2.19 (m, 8H), 2.10 (m, 2H), 2.01 (m, 2H), 1.96 (t, J = 2.6 Hz, 1H), 1.68 - 1.59 (m, 6H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 144.7, 134.0, 124.9, 106.6, 97.7, 84.4, 68.4, 55.2, 38.4, 36.3, 29.7, 17.6, 15.8.

HRMS-ESI calculated for $C_{19}H_{30}NaO_2$ $[M+Na]^+$: 313.2138; found: 313.2136.

(4*E*,8*E*)-5,9-Dimethyltrideca-4,8-dien-12-yn-1-ol (188)



52 Huang, J.; Wu, C.; Wulff, W. D. *J. Am. Chem. Soc*. **2007**, *129*, 13366−13367.

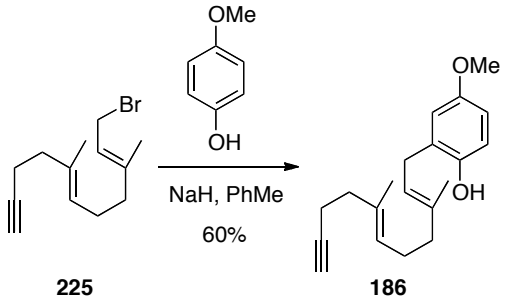
A solution of **226** (100 mg, 0.34 mmol) in Et_2O (4 mL) was added dropwise to a solution of $LiAlH_4$ (26.2 mg, 0.69 mmol) in Et_2O (2 mL) at 0 °C and the mixture was kept at this temperature for 1 h before it was quenched with 10% aqueous NaOH (10 mL) at 0 °C. The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 8:1) to give **188** (65 mg, 86%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (m, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.33 - 2.26 (m, 2H), 2.25 - 2.20 (m, 2H), 2.15 - 2.07 (m, 4H), 2.03 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.68 - 1.61 (m, 8H), 1.40 (br m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.3, 125.5, 123.9, 84.4, 68.3, 62.7, 39.5, 38.4, 32.7, 26.5, 24.3, 17.6, 16.0, 15.8.

HRMS-APCI calculated for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900; found: 221.1896.

2-((2*E*,6*E*)-3,7-Dimethylundeca-2,6-dien-10-yn-1-yl)-4-methoxyphenol (186)



225 **186**

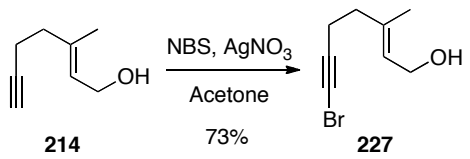
NaH (10.8 mg, 60% dispersion in mineral oil, 0.27 mmol) was added to a solution of 4-methoxyphenol (33.5 mg, 0.27 mmol) in PhMe (2 mL) at 23 °C and the mixture was stirred at this temperature for 15 minutes. A solution of **225** (64 mg, 0.25 mmol) in PhMe (1 mL) was added and the reaction mixture was stirred at 23 °C for 15 h before it was quenched with water (5 mL). The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 7:1) to give **186** (45 mg, 60%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, J = 8.5, 0.6 Hz, 1H), 6.72 - 6.66 (m, 2H), 5.33 (tq, J = 7.2, 1.3 Hz, 1H), 5.18 (dddd, J = 6.8, 5.4, 2.7, 1.2 Hz, 1H), 4.79 (s, 1H), 3.78 (s, 3H), 3.35 (d, J = 7.2 Hz, 2H), 2.32 - 2.25 (m, 2H), 2.25 - 2.08 (m, 6H), 1.96 (t, J = 2.5 Hz, 1H), 1.79 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 148.2, 138.3, 133.8, 128.1, 125.0, 121.6, 116.3, 115.7, 112.0, 84.5, 68.3, 55.7, 39.5, 38.3, 29.9, 26.3, 17.5, 16.2, 15.9.

HRMS-ESI calculated for $C_{20}H_{26}NaO_2$ $[M+Na]^+$: 321.1830; found: 321.1821.

(*E*)-7-Bromo-3-methylhept-2-en-6-yn-1-ol (227)



214 **227**

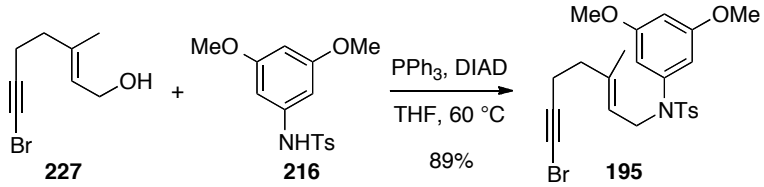
N-bromosuccinimide (117 mg, 0.66 mmol) and silver nitrate (11.2 mg, 66 μmol) were added sequentially to a solution of **214** (74.2 mg, 0.6 mmol) in acetone (2 mL) at 23 °C and the resulting mixture was stirred at this temperature for 1 h. The solvent was evaporated and the residue was taken up in Et_2O (10 mL) and washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 4:1) to give **227** (88.7 mg, 73%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (tdd, J = 6.9, 2.7, 1.3 Hz, 1H), 4.18 (d, J = 6.9 Hz, 2H), 2.40 - 2.30 (m, 2H), 2.25 (m, 2H), 1.69 (s, 3H), 1.31 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 124.8, 79.6, 59.3, 38.4, 37.9, 18.5, 16.1.

HRMS-ESI calculated for $C_8H_{11}BrNaO$ $[M+Na]^+$: 224.9885; found: 224.9888.

(*E*)-*N*-(7-Bromo-3-methylhept-2-en-6-yn-1-yl)-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (195)



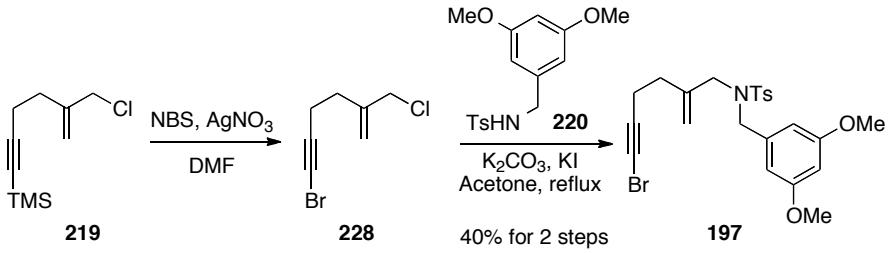
195 can be prepared by the same method as **168** from **227** and **216**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.55 (m, 2H), 7.32 - 7.23 (m, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.22 (d, J = 2.3 Hz, 2H), 5.18 (tq, J = 6.9, 1.2 Hz, 1H), 4.20 - 4.10 (m, 2H), 3.73 (s, 6H), 2.45 (s, 3H), 2.22 - 2.16 (m, 2H), 2.12 (dd, J = 8.6, 5.2 Hz, 2H), 1.56 - 1.53 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 143.4, 141.2, 138.4, 135.7, 129.4, 127.8, 120.1, 107.0, 100.1, 79.5, 55.4, 48.5, 38.3, 37.8, 21.6, 18.6, 16.2.

HRMS-ESI calculated for $C_{23}H_{26}BrNNaO_4S$ $[M+Na]^+$: 514.0653; found: 514.0658.

***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-methylbenzenesulfonamide (197)**



N-bromosuccinimide (100.7 mg, 0.56 mmol) and silver nitrate (8.7 mg, 0.05 mmol) were added sequentially to a solution of **219** (103.4 mg, 0.51 mmol) in DMF (2 mL) at 23 °C and the resulting mixture was stirred at this temperature for 1 h. The mixture was diluted with water (10 mL) and extracted with Et_2O (10 mL). The organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated to give **228** as colorless oil which was used without further purification.

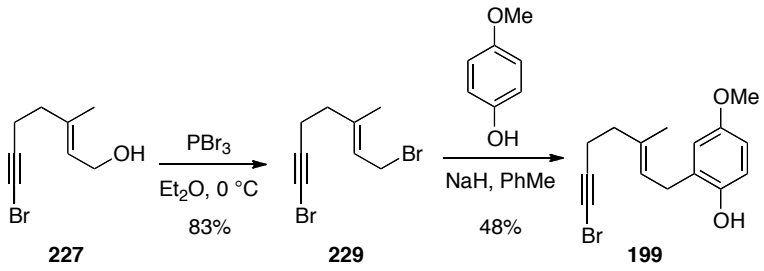
To a solution of **228** (62.3 mg, 0.3 mmol) and **220** (115.6 mg, 0.36 mmol) in acetone (5 mL) was added K_2CO_3 (49.7 mg, 0.36 mmol) and KI (5.0 mg, 0.03 mmol) at 23 °C. The mixture was set to reflux for 24 h before the solvent was evaporated. The residue was taken up in Et_2O (10 mL) and washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 5:1) to give **197** (100 mg, 40% from) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 - 7.72 (m, 2H), 7.35 - 7.31 (m, 2H), 6.35 (t, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 2H), 4.92 (d, J = 1.5 Hz, 1H), 4.87 (d, J = 1.4 Hz, 1H), 4.28 (s, 2H), 3.73 (s, 2H), 3.72 (s, 6H), 2.45 (s, 3H), 2.24 (td, J = 7.2, 1.0 Hz, 2H), 2.10 (t, J = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 143.4, 141.7, 138.2, 137.4, 129.7, 127.2, 115.3, 106.4, 99.9, 79.4, 55.3, 52.1, 51.0, 38.4, 31.4, 21.5, 18.0.

HRMS-ESI calculated for $C_{23}H_{26}BrNNaO_4S$ $[M+Na]^+$: 514.0658; found: 514.0652.

(*E*)-2-(7-Bromo-3-methylhept-2-en-6-yn-1-yl)-4-methoxyphenol (199)



229 can be prepared by the same method as **215** from **227**.

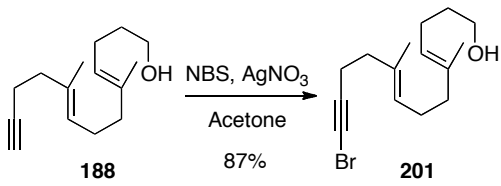
199 can be prepared by the same method as **186** from **229** and 4-methoxyphenol.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 3.2 Hz, 1H), 6.68 (dd, J = 8.6, 3.1 Hz, 1H), 5.40 (tq, J = 7.2, 1.3 Hz, 1H), 4.68 (s, 1H), 3.78 (s, 3H), 3.37 (d, J = 7.1 Hz, 2H), 2.40 - 2.35 (m, 2H), 2.29 (m, 2H), 1.79 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 148.0, 136.1, 128.0, 123.1, 116.4, 115.7, 112.1, 79.6, 55.7, 38.6, 38.1, 29.7, 18.7, 16.0.

HRMS-ESI calculated for $C_{15}H_{17}BrNaO_2$ $[M+Na]^+$: 331.0311; found: 331.0317.

(4*E*,8*E*)-13-Bromo-5,9-dimethyltrideca-4,8-dien-12-yn-1-ol (201)



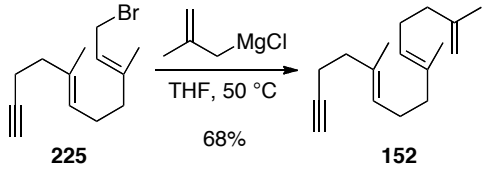
201 can be prepared by the same method as **227** from **188**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (m, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.34 - 2.27 (m, 2H), 2.24 - 2.18 (m, 2H), 2.15 - 2.06 (m, 4H), 2.06 - 2.00 (m, 2H), 1.72 - 1.63 (m, 2H), 1.64 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 133.1, 125.7, 123.9, 80.1, 62.8, 39.5, 38.2, 37.9, 32.8, 26.5, 24.3, 18.9, 16.0, 15.8.

HRMS-ESI calculated for $C_{15}H_{23}BrNaO$ $[M+Na]^+$: 321.0832; found: 321.0836.

(5*E*,9*E*)-2,6,10-Trimethyltetradeca-1,5,9-trien-13-yne (152)



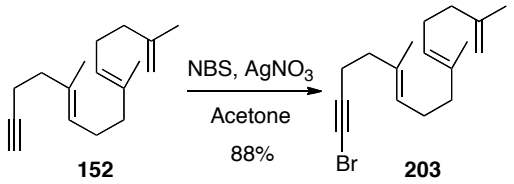
To a solution of **225** (368 mg, 1.44 mmol) in THF (10 mL) was added (2-methylallyl)magnesium chloride (4.3 mL, 0.5 M in THF, 2.16 mmol) at 0 °C and the mixture was stirred at 50 °C for 8 h before it was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (5 mL) and the combined organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane) to give **152** (225 mg, 68%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (ddq, J = 7.0, 5.6, 1.3 Hz, 1H), 5.15 (tq, J = 6.9, 1.3 Hz, 1H), 4.74 (ddq, J = 2.8, 2.0, 0.9 Hz, 1H), 4.71 (dq, J = 2.1, 1.1 Hz, 1H), 2.29 (tdd, J = 6.9, 2.5, 1.1 Hz, 2H), 2.23 (ddt, J = 8.3, 7.0, 1.3 Hz, 2H), 2.19 - 2.09 (m, 4H), 2.09 - 2.00 (m, 4H), 1.97 (t, J = 2.5 Hz, 1H), 1.76 - 1.74 (s, 3H), 1.65 - 1.62 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 135.0, 133.1, 125.6, 124.2, 109.8, 84.5, 68.3, 39.5, 38.4, 37.8, 26.5, 26.2, 22.5, 17.6, 16.0, 15.8.

HRMS-APCI calculated for $C_{17}H_{27}$ $[M+H]^+$: 231.2107; found: 231.2100.

(5*E*,9*E*)-14-Bromo-2,6,10-trimethyltetradeca-1,5,9-trien-13-yne (203)



152 **203**

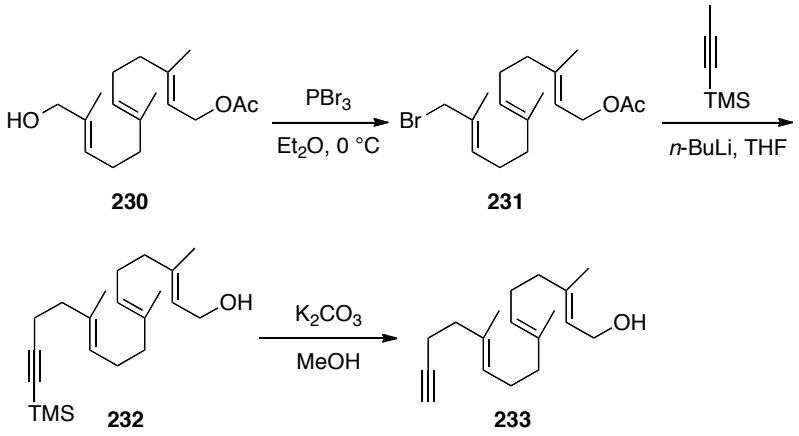
203 can be prepared by the same method as **227** from **152**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 - 5.09 (m, 2H), 4.72 (ddd, J = 11.6, 2.3, 1.2 Hz, 2H), 2.30 (m, 2H), 2.23 - 1.99 (m, 10H), 1.75 (s, 3H), 1.63 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 135.0, 132.9, 125.8, 124.2, 109.8, 80.1, 39.5, 38.2, 37.9, 37.8, 26.5, 26.2, 22.5, 18.9, 16.0, 15.8.

HRMS-APCI calculated for $C_{17}H_{26}Br$ $[M+H]^+$: 309.1212; found: 309.1216.

(2*E*,6*E*,10*E*)-3,7,11-Trimethylpentadeca-2,6,10-trien-14-yn-1-ol (233)



231 can be prepared by the same method as **215** from **230**[53] (2.04 g, 7.3 mmol).

n-BuLi (11.7 mL, 2.5 M in hexanes, 29.2 mmol) was added dropwise to a solution of 1-(trimethylsilyl)propyne (4.3 mL, 29.2 mmol) in THF (80 mL) at -40 °C and the mixture was kept at this temperature for 45 minutes before it was cooled to -60 °C and a solution of **231** (prepared in the last step) in THF (20 mL) was added and the reaction mixture was stirred at -60 °C for 1 h before it was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O and the combined organic layer was washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to the next step without further purification.

K_2CO_3 (4.03 g, 29.2 mmol) was added to a solution of the residue above in MeOH (40 mL) at 23 °C and the mixture was stirred at this temperature for 12 h. The solvent was evaporated and the residue was taken up in Et_2O (20 mL) and washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 7:1) to give **233** (930 mg, 49% for three steps) as colorless oil.

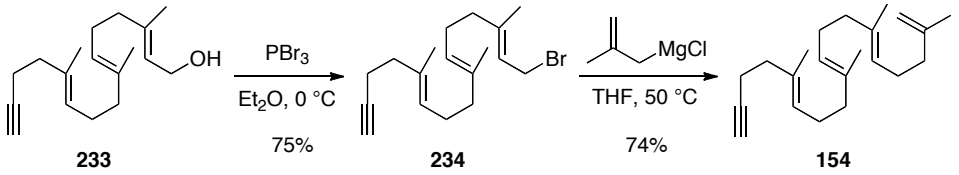
53 Suhara, Y.; Hirota, Y.; Nakagawa, K.; Kamao, M.; Tsugawa, N.; Okano, T. *Bioorg. Med. Chem*. **2008**, *16*, 3108−3117.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (m, 1H), 5.20 (m, 1H), 5.14 (m, 1H), 4.18 (d, J = 6.9 Hz, 2H), 2.29 (m, 2H), 2.26 - 2.20 (m, 2H), 2.18 - 1.99 (m, 8H), 1.97 (t, J = 2.5 Hz, 1H), 1.71 (s, 3H), 1.63 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 135.2, 133.2, 125.5, 123.9, 123.4, 84.4, 77.2, 68.3, 59.4, 39.5, 38.4, 26.6, 26.3, 17.6, 16.3, 16.0, 15.8.

HRMS-APCI calculated for $C_{18}H_{29}O$ $[M+H]^+$: 261.2218; found: 261.2215.

(5*E*,9*E*,13*E*)-2,6,10,14-Tetramethyloctadeca-1,5,9,13-tetraen-17-yne (154)



233 **234** **154**

234 can be prepared by the same method as **215** from **233**.

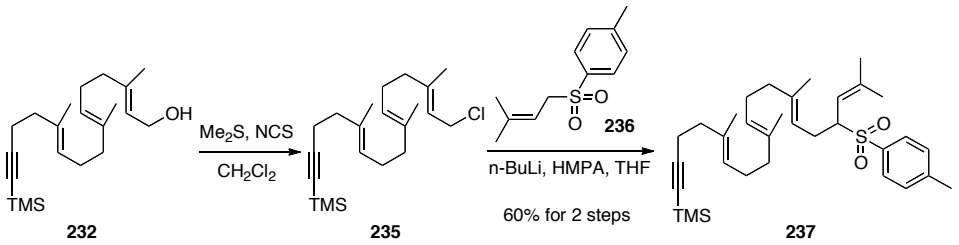
154 can be prepared by the same method as **152** from **234**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 - 5.11 (m, 3H), 4.74 - 4.69 (m, 2H), 2.33 - 2.26 (m, 2H), 2.25 - 2.21 (m, 2H), 2.17 - 1.98 (m, 12H), 1.96 (t, J = 2.5 Hz, 1H), 1.75 (s, 3H), 1.63 (s, 6H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 135.1, 134.7, 133.1, 125.6, 124.4, 124.1, 109.7, 84.4, 68.3, 39.7, 39.6, 38.4, 37.8, 26.6, 26.2, 22.5, 17.6, 16.0, 15.8.

HRMS-APCI calculated for $C_{22}H_{35}$ $[M+H]^+$: 299.2733; found: 299.2745.

Trimethyl((5*E*,9*E*,13*E*)-5,9,13,18-tetramethyl-16-tosylnonadeca-5,9,13,17-tetraen-1-yn-1-yl)silane (237)



232 **235** **237**

Dimethyl sulfide (0.28 mL, 3.75 mmol) was added to a solution of *N*-chlorosuccinimide (459 mg, 3.44 mmol) in CH_2Cl_2 (10 mL) at -30 °C and the reaction mixture was stirred at this temperature for 15 minutes. The a solution of **232** (1.04 g, 3.13 mmol) in CH_2Cl_2 (5 mL) was added slowly and the reaction mixture was allowed to warm to room temperature and stirred for another 2 h. the reaction was quenched by the addition of water (20 mL) and and the organic layer was washed sequentially with water (20×3 mL) and brine (20 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to the next step without further purification.

n-BuLi (1.5 mL, 2.5 M in hexanes, 3.76 mmol) and hexamethylphosphoramide (0.71 mL, 4.07 mmol) was added sequentially to a solution of **236**[54] (701 mg, 3.13 mmol) in THF (8 mL) at -20 °C and the mixture was kept at this temperature for 30 minutes before it was cooled to -78 °C and a solution of **235** (prepared in the last step) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for 1 h. The cooling bath was removed and the mixture was stirred at room temperature for another 1 h before it was quenched with saturated aqueous NH_4Cl (40 mL). The aqueous layer was extracted with Et_2O (30 mL) and the combined organic layer was washed sequentially with water (40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to give **237** (1.01 g, 60% for 2 steps) as colorless oil.

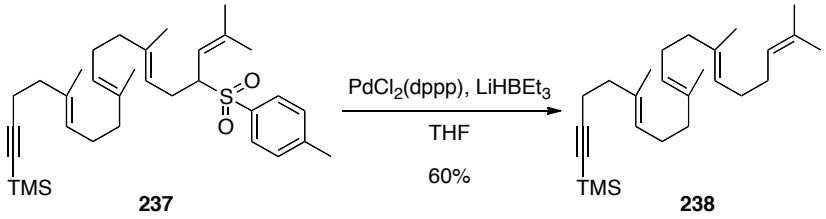
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.70 (m, 2H), 7.34 - 7.30 (m, 2H), 5.19 - 5.13 (m, 1H), 5.07 (tt, J = 5.6, 3.0 Hz, 1H), 4.98 (dddd, J = 7.5, 4.7, 3.0, 1.5 Hz, 2H), 3.70 (td, J = 10.6, 3.4 Hz, 1H), 2.89 - 2.79 (m, 1H), 2.45 (s, 3H), 2.39 - 2.25 (m, 3H), 2.19 (dd, J = 8.3, 6.7 Hz, 2H), 2.12 - 1.93 (m, 8H), 1.69 (d, J = 1.5 Hz, 3H), 1.63 - 1.57 (m, 9H), 1.23 (d, J = 1.4 Hz, 3H), 0.15 (s, 9H).

54 Wu, B.; Woodward, R.; Wen, L.; Wang, X.; Zhao, G.; Wang, P. G. *Eur. J. Org. Chem*. **2013**, 8162−8173.

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 141.5, 138.5, 135.2, 135.0, 133.4, 129.3, 129.1, 125.5, 124.0, 118.7, 117.3, 107.4, 84.5, 65.0, 39.7, 39.6, 38.7, 26.6, 26.6, 26.6, 25.8, 21.6, 19.2, 18.1, 16.4, 16.0, 15.8, 0.2.

HRMS-APCI calculated for $C_{33}H_{51}O_2SSi$ $[M+H]^+$: 539.3379; found: 539.3376.

Trimethyl((5*E*,9*E*,13*E*)-5,9,13,18-tetramethylnonadeca-5,9,13,17-tetraen-1-yn-1-yl)silane (238)



237 **238**

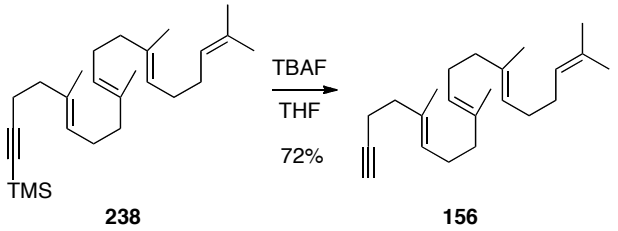
To a solution of **237** (812 mg, 1.51 mmol) in THF (15 mL) was added $PdCl_2$(dppp) (89 mg, 0.151 mmol) at 0 °C. Lithium triethylborohydride ($LiHBEt_3$, 1.0 M solution in THF, 5 mL, 5.0 mmol) was then added slowly to the solution over a 1 min period. The reaction mixture was stirred for an additional 4 h at 0 °C and then diluted with Et_2O (20 mL), followed by the addition of saturated NH_4Cl (40 mL).. The organic layer was washed sequentially with water (40 mL×2), and brine (40 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane) to give **238** (349 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 - 5.10 (m, 4H), 2.32 (ddd, J = 7.8, 6.9, 1.2 Hz, 2H), 2.24 - 2.18 (m, 2H), 2.14 - 2.06 (m, 4H), 2.06 - 1.97 (m, 8H), 1.71 (d, J = 1.5 Hz, 3H), 1.64 - 1.61 (m, 12H), 0.17 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 134.8, 133.3, 131.4, 125.6, 124.5, 124.4, 124.3, 107.4, 84.5, 39.7, 39.6, 38.7, 28.4, 28.3, 26.6, 25.7, 19.2, 17.7, 16.0, 16.0, 15.8, 0.2.

HRMS-APCI calculated for $C_{26}H_{45}Si$ $[M+H]^+$: 385.3290; found: 385.3296.

(5*E*,9*E*,13*E*)-5,9,13,18-Tetramethylnonadeca-5,9,13,17-tetraen-1-yne (156)



238 **156**

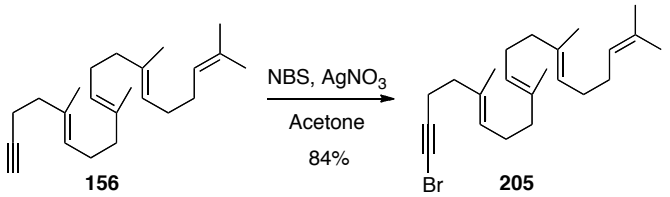
156 can be prepared by the same method as **181** from **238**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 - 5.12 (m, 4H), 2.30 (dddd, J = 7.9, 6.8, 2.5, 1.6 Hz, 2H), 2.25 - 2.20 (m, 2H), 2.15 - 2.07 (m, 4H), 2.05 - 1.99 (m, 8H), 1.96 (t, J = 2.6 Hz, 1H), 1.71 (d, J = 1.5 Hz, 3H), 1.64 – 1.62 (m, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 134.7, 133.1, 131.4, 125.6, 124.5, 124.4, 124.3, 84.4, 68.3, 39.7, 39.6, 38.4, 28.4, 28.3, 26.6, 26.6, 25.7, 17.7, 17.6, 16.0, 16.0, 15.8.

HRMS-APCI calculated for $C_{23}H_{37}$ $[M+H]^+$: 313.2895; found: 313.2899.

(5*E*,9*E*,13*E*)-1-Bromo-5,9,13,18-tetramethylnonadeca-5,9,13,17-tetraen-1-yne (205)



156 **205**

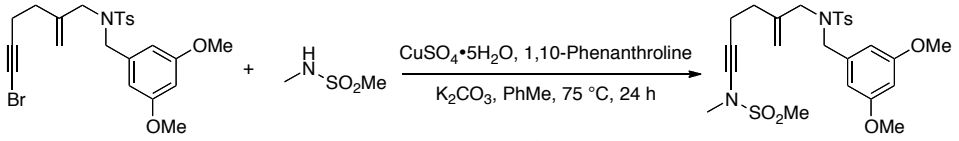
205 can be prepared by the same method as **227** from **156**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 - 5.10 (m, 4H), 2.36 - 2.25 (m, 2H), 2.25 - 2.16 (m, 2H), 2.15 - 2.06 (m, 4H), 2.06 - 1.98 (m, 8H), 1.71 (s, 3H), 1.63 (m, 15H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 134.7, 132.9, 131.5, 125.8, 124.5, 124.4, 124.3, 80.1, 39.7, 39.5, 38.2, 37.9, 28.4, 28.3, 26.7, 26.6, 25.7, 18.9, 17.7, 16.0, 16.0, 15.8.

HRMS-ESI calculated for $C_{23}H_{35}BrNa$ $[M+Na]^+$: 413.1822; found: 413.1825.

N-(3,5-Dimethoxybenzyl)-4-methyl-*N*-(2-methylene-6-(*N*-methylmethylsulfonamido)hex-5-yn-1-yl)benzenesulfonamide (212)



197 **212**

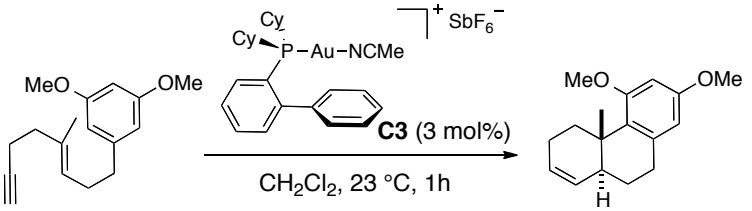
Degassed toluene (3 mL) was added to a 10 ml microwave vial containing **197** (89 mg, 0.18 mmol), *N*-methylmethanesulfonamide (19.7 mg, 0.18 mmol), $CuSO_4$•$5H_2O$ (4.5 mg, 0.02 mmol), 1,10-phenanthroline (6.5 mg, 0.04 mmol) and K_2CO_3 (50 mg, 0.36 mmol). The vial was purged with Argon and then fitted with a septa and vial seal. The reaction was then heated to 75 °C for 24 hours. The reaction mixture was purified by flash column chromatography (cyclohexane/EtOAc 2:1) to give **212** (79 mg, 84%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 - 7.69 (m, 2H), 7.35 - 7.31 (m, 2H), 6.33 (t, J = 2.3 Hz, 1H), 6.25 (d, J = 2.3 Hz, 2H), 4.96 - 4.93 (m, 1H), 4.89 (d, J = 1.7 Hz, 1H), 4.27 (s, 2H), 3.75 (s, 2H), 3.69 (s, 6H), 3.14 (s, 3H), 3.02 (s, 3H), 2.44 (s, 3H), 2.35 (t, J = 7.2 Hz, 2H), 2.15 (dd, J = 7.8, 6.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 143.4, 142.1, 138.2, 137.4, 129.7, 127.2, 115.1, 106.4, 99.9, 74.9, 68.3, 55.3, 52.2, 51.0, 39.1, 36.0, 32.1, 21.5, 16.8.

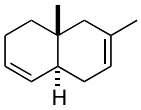
HRMS-ESI calculated for $C_{25}H_{32}N_2NaO_6S_2$ $[M+Na]^+$: 543.1599; found: 543.1596.

Representative procedure for gold(I)-catalyzed polycyclizations



166 95% **167**

C3 (4.9 mg, 6 μmol) was added to a solution of **166** (51.6 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at 23 °C for 1 h. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to give **167** (49 mg, 95%) as colorless oil.

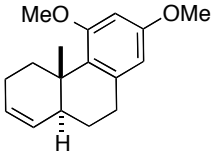


151

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 - 5.60 (m, 1H), 5.43 - 5.36 (m, 2H), 2.18 - 1.93 (m, 4H), 1.91 - 1.82 (m, 1H), 1.78 - 1.63 (m, 2H), 1.68 (m, 3H), 1.54 - 1.37 (m, 2H), 0.81 - 0.78 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.4, 130.2, 126.1, 120.5, 45.9, 39.5, 36.7, 31.0, 28.7, 24.0, 23.2, 15.8.

HRMS-ESI calculated for $C_{12}H_{19}$ $[M+H]^+$: 163.1488; found: 163.1494.

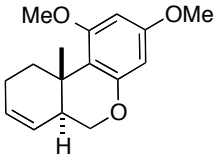


167

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 2.6 Hz, 1H), 6.27 (dt, J = 2.6, 0.8 Hz, 1H), 5.70 (dq, J = 9.9, 3.7 Hz, 1H), 5.48 (dq, J = 9.7, 2.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.16 (ddt, J = 13.2, 6.6, 1.3 Hz, 1H), 3.01 (dddt, J = 17.1, 12.1, 7.1, 1.0 Hz, 1H), 2.87 - 2.77 (m, 1H), 2.41 (dddd, J = 12.3, 6.1, 3.1, 1.9 Hz, 1H), 2.34 - 2.12 (m, 2H), 1.75 (tdd, J = 13.1, 12.1, 5.7 Hz, 1H), 1.64 (ddt, J = 8.7, 4.2, 1.4 Hz, 1H), 1.54 - 1.44 (m, 1H), 1.18 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 158.0, 139.0, 131.2, 127.8, 127.0, 105.2, 97.3, 55.1, 55.0, 44.0, 36.5, 32.4, 32.3, 24.6, 24.5, 17.0.

HRMS-ESI calculated for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1693; found: 259.1687.

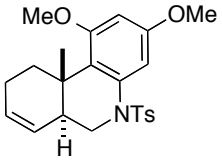


169

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 - 6.00 (m, 2H), 5.84 - 5.76 (m, 1H), 5.38 (dq, J = 9.8, 2.2 Hz, 1H), 4.10 (dd, J = 10.3, 4.0 Hz, 1H), 3.99 (dd, J = 12.5, 10.3 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.10 - 3.01 (m, 1H), 2.71 (ddqd, J = 12.8, 5.8, 3.4, 1.9 Hz, 1H), 2.29 - 2.18 (m, 2H), 1.56 - 1.49 (m, 1H), 1.18 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 159.1, 155.7, 129.2, 123.6, 113.6, 94.0, 92.1, 66.2, 55.2, 55.2, 41.5, 33.2, 31.8, 24.2, 17.9.

HRMS-ESI calculated for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485; found: 261.1473.



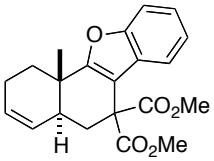
171

M.p.: 111-112 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.24 - 7.18 (m, 3H), 6.24 (d, J = 2.5 Hz, 1H), 5.73 (dq, J = 9.9, 3.3 Hz, 1H), 5.35 (dq, J = 9.8, 2.1 Hz, 1H), 4.02 (dd, J = 11.9, 4.3 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.24 (dd, J = 13.6, 11.9 Hz, 1H), 3.00 (dt, J = 13.4, 4.4 Hz, 1H), 2.38 (s, 3H), 2.35 - 2.31 (m, 1H), 2.09 (m, 2H), 1.29 (m, 1H), 0.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 158.1, 143.7, 137.8, 135.7, 129.5, 128.6, 127.3, 124.9, 120.3, 100.3, 96.1, 55.3, 55.3, 47.7, 40.9, 35.0, 31.8, 23.7, 21.5, 16.3.

HRMS-ESI calculated for $C_{23}H_{27}NNaO_4S$ $[M+Na]^+$: 436.1553; found: 436.1533.

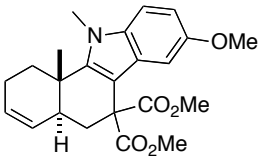


173

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 - 7.52 (m, 1H), 7.47 - 7.42 (m, 1H), 7.26 - 7.20 (m, 2H), 5.73 (ddd, J = 10.2, 4.3, 2.7 Hz, 1H), 5.56 (dq, J = 9.9, 2.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.76 (dd, J = 14.0, 4.9 Hz, 1H), 2.66 (dd, J = 13.6, 2.6 Hz, 1H), 2.37 - 2.16 (m, 4H), 1.82 - 1.70 (m, 1H), 1.23 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 170.8, 163.7, 154.4, 127.6, 127.4, 123.2, 122.6, 121.3, 111.1, 107.7, 55.2, 52.9, 52.7, 40.0, 34.5, 32.6, 30.6, 22.9, 18.3.

HRMS-ESI calculated for $C_{21}H_{22}NaO_5$ $[M+Na]^+$: 377.1359; found: 377.1373.



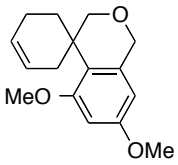
175

M.p.: 165-168 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.9 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.9, 2.5 Hz, 1H), 5.76 (dq, J = 9.9, 3.3 Hz, 1H), 5.56 (dq, J = 9.9, 2.1 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 2.78 (m, 1H), 2.61 (m, 2H), 2.35 - 2.23 (m, 3H), 1.86 (m, 1H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 171.8, 154.2, 145.9, 133.1, 129.1, 126.9, 126.5, 111.1, 109.4, 104.6, 103.2, 56.3, 56.1, 52.7, 52.6, 41.3, 35.3, 33.2, 32.7, 32.1, 23.6, 17.5.

HRMS-ESI calculated for $C_{23}H_{28}NO_5$ $[M+H]^+$: 398.1962; found: 398.1963.

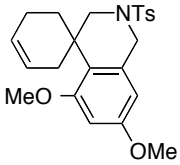


182

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, J = 2.5 Hz, 1H), 6.20 - 6.09 (m, 1H), 5.73 (s, 2H), 4.77 - 4.63 (m, 2H), 3.95 (d, J = 11.4 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.62 (dd, J = 11.3, 1.3 Hz, 1H), 2.90 - 2.82 (m, 1H), 2.75 (ddd, J = 13.3, 10.2, 9.1 Hz, 1H), 2.12 - 2.01 (m, 3H), 1.50 - 1.42 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 158.6, 137.5, 126.4, 125.4, 122.5, 99.9, 98.1, 73.8, 70.0, 55.2, 55.0, 34.5, 31.5, 27.4, 22.0.

HRMS-ESI calculated for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485; found: 261.1475.



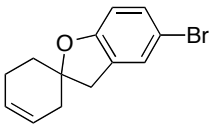
183

M.p.: 176-178 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.39 - 7.35 (m, 2H), 6.35 (d, J = 2.5 Hz, 1H), 6.20 - 6.16 (m, 1H), 5.80 - 5.74 (m, 1H), 5.74 - 5.67 (m, 1H), 4.24 - 4.16 (m, 1H), 4.04 (dd, J = 14.5, 1.1 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.19 (dd, J = 11.5, 1.5 Hz, 1H), 3.04 - 2.96 (m, 2H), 2.70 (ddd, J = 13.3, 11.8, 6.5 Hz, 1H), 2.46 (s, 3H), 2.18 (m, 1H), 2.13 - 2.02 (m, 1H), 1.94 (ddd, J = 18.5, 4.2, 2.2 Hz, 1H), 1.52 - 1.44 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.6, 143.6, 134.3, 133.0, 129.7, 127.9, 125.9, 125.3, 122.8, 102.1, 98.5, 55.2, 55.1, 52.4, 50.0, 36.9, 31.8, 27.7, 21.9, 21.5.

HRMS-ESI calculated for $C_{23}H_{27}NNaO_4S$ $[M+Na]^+$: 436.1553; found: 436.1558.

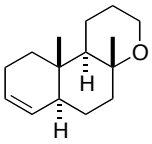


191

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.20 (m, 2H), 6.66 (d, J = 8.4 Hz, 1H), 5.80 (m, 1H), 5.66 (m, 1H), 3.07 - 2.95 (m, 2H), 2.52 - 2.28 (m, 3H), 2.25 - 2.14 (m, 1H), 2.01 (dtd, J = 12.9, 6.3, 1.2 Hz, 1H), 1.81 (dtd, J = 12.9, 6.4, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 130.7, 129.1, 128.1, 126.8, 123.8, 111.6, 111.1, 87.6, 40.8, 37.1, 32.4, 23.4.

HRMS-APCI calculated for $C_{13}H_{14}BrO$ $[M+H]^+$: 265.0223; found: 265.0219.

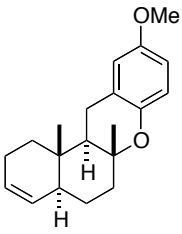


189

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (dq, J = 9.9, 3.2 Hz, 1H), 5.35 (dq, J = 9.8, 2.1 Hz, 1H), 3.75 (ddd, J = 11.9, 9.6, 7.0 Hz, 1H), 3.70 - 3.63 (m, 1H), 2.09 (dh, J = 6.7, 3.2, 2.3 Hz, 2H), 2.00 (dddd, J = 14.1, 4.8, 3.3, 1.4 Hz, 1H), 1.81 - 1.64 (m, 5H), 1.59 - 1.38 (m, 4H), 1.36 - 1.26 (m, 4H), 1.22 - 1.13 (m, 1H), 0.66 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.3, 125.8, 75.0, 61.0, 55.1, 46.2, 41.2, 35.0, 34.4, 27.7, 25.6, 23.2, 20.7, 18.3, 11.6.

HRMS-APCI calculated for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900; found: 221.1890.

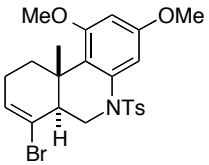


187

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 - 6.67 (m, 2H), 6.65 (dd, J = 2.8, 1.0 Hz, 1H), 5.60 (dq, J = 9.9, 3.5 Hz, 1H), 5.42 (dq, J = 9.8, 2.0 Hz, 1H), 3.77 (s, 3H), 2.75 (dd, J = 16.4, 5.2 Hz, 1H), 2.70 - 2.63 (m, 1H), 2.17 - 2.11 (m, 2H), 2.08 (ddt, J = 12.6, 10.3, 3.1 Hz, 2H), 1.86 - 1.79 (m, 1H), 1.79 - 1.71 (m, 2H), 1.63 (ddt, J = 13.9, 4.3, 3.1 Hz, 1H), 1.48 (td, J = 13.4, 3.3 Hz, 1H), 1.34 - 1.30 (m, 1H), 1.29 (d, J = 1.0 Hz, 3H), 0.83 (d, J = 0.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 147.4, 130.1, 125.8, 123.0, 117.6, 114.3, 113.1, 55.7, 49.4, 45.9, 40.4, 34.9, 34.8, 25.2, 23.1, 23.0, 21.4, 11.4.

HRMS-ESI calculated for $C_{20}H_{26}NaO_2$ $[M+Na]^+$: 321.1825; found: 321.1810.

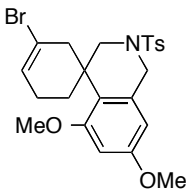


196

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 - 7.59 (m, 2H), 7.27 - 7.23 (m, 2H), 7.22 (d, J = 2.5 Hz, 1H), 6.28 (d, J = 2.5 Hz, 1H), 6.11 (dt, J = 5.4, 3.0 Hz, 1H), 4.68 (dd, J = 13.0, 3.5 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.27 (t, J = 12.8 Hz, 1H), 3.09 - 3.00 (m, 1H), 2.46 - 2.42 (m, 1H), 2.40 (s, 3H), 2.22 - 2.12 (m, 1H), 2.08 (dtdd, J = 13.8, 7.8, 3.9, 2.3 Hz, 1H), 1.18 (ddd, J = 13.5, 11.6, 6.6 Hz, 1H), 0.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.4, 143.8, 137.8, 136.2, 130.6, 129.6, 127.3, 120.9, 119.0, 100.7, 96.6, 55.4, 55.3, 47.1, 46.2, 38.1, 31.3, 25.8, 21.6, 17.2.

HRMS-ESI calculated for $C_{23}H_{26}BrNNaO_4S$ $[M+Na]^+$: 514.0658; found: 514.0651.

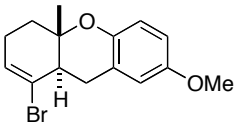


198

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 - 7.74 (m, 2H), 7.41 - 7.37 (m, 2H), 6.35 (d, J = 2.5 Hz, 1H), 6.18 (d, J = 2.5 Hz, 1H), 6.13 - 6.09 (m, 1H), 4.18 (d, J = 14.5 Hz, 1H), 4.09 (d, J = 14.4 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.51 (ddt, J = 18.0, 4.6, 2.5 Hz, 1H), 3.23 (d, J = 12.0 Hz, 1H), 2.98 (d, J = 11.9 Hz, 1H), 2.64 - 2.54 (m, 1H), 2.47 (s, 3H), 2.36 - 2.25 (m, 1H), 2.25 - 2.19 (m, 1H), 2.19 - 2.11 (m, 1H), 1.61 - 1.57 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 159.0, 143.8, 134.4, 133.0, 129.8, 127.8, 127.0, 121.0, 120.8, 102.2, 98.4, 55.3, 55.2, 52.2, 49.8, 41.4, 39.6, 26.3, 24.0, 21.6.

HRMS-ESI calculated for $C_{23}H_{26}BrNNaO_4S$ $[M+Na]^+$: 514.0658; found: 514.0664.

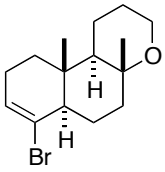


200

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 9.0, 3.0 Hz, 1H), 6.71 - 6.69 (m, 1H), 6.12 (dt, J = 5.0, 2.9 Hz, 1H), 3.79 (s, 3H), 3.07 (dd, J = 16.3, 5.3 Hz, 1H), 2.90 - 2.82 (m, 1H), 2.61 (ddt, J = 16.2, 13.6, 1.0 Hz, 1H), 2.37 - 2.18 (m, 2H), 2.01 (m, 1H), 1.93 (m, 1H), 1.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 147.1, 129.1, 123.7, 122.5, 117.8, 114.2, 114.0, 76.0, 55.7, 45.0, 34.8, 28.9, 25.7, 16.3.

HRMS-ESI calculated for $C_{15}H_{17}BrNaO_2$ $[M+Na]^+$: 331.0311; found: 331.0314.

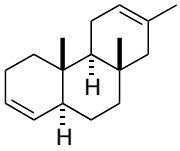


202

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dt, J = 4.3, 3.3 Hz, 1H), 3.77 - 3.70 (m, 1H), 3.69 - 3.64 (m, 1H), 2.35 - 2.28 (m, 1H), 2.16 - 2.10 (m, 3H), 1.84 - 1.75 (m, 2H), 1.70 - 1.66 (m, 2H), 1.46 - 1.41 (m, 2H), 1.37 - 1.33 (m, 1H), 1.34 (d, J = 0.9 Hz, 3H), 1.30 - 1.27 (m, 1H), 1.24 - 1.21 (m, 1H), 0.75 (d, J = 0.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.2, 126.9, 74.5, 60.9, 54.8, 51.2, 41.0, 37.9, 33.8, 27.5, 25.3, 25.1, 20.5, 18.6, 11.9.

HRMS-ESI calculated for $C_{15}H_{23}BrNaO$ $[M+Na]^+$: 321.0832; found: 321.0838.

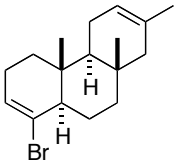


153

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddt, J = 10.0, 4.3, 3.2 Hz, 1H), 5.38 (ddt, J = 9.8, 4.2, 1.8 Hz, 2H), 2.08 (dddd, J = 10.2, 7.1, 4.2, 2.1 Hz, 3H), 1.90 (ddddd, J = 15.3, 13.9, 6.4, 3.5, 2.0 Hz, 3H), 1.78 - 1.71 (m, 1H), 1.67 - 1.60 (m, 4H), 1.58 - 1.54 (m, 1H), 1.51 (dd, J = 13.1, 3.0 Hz, 1H), 1.41 - 1.34 (m, 1H), 1.31 - 1.25 (m, 1H), 1.22 - 1.16 (m, 1H), 1.16 - 1.10 (m, 1H), 0.96 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.2, 131.4, 125.4, 120.2, 51.6, 49.9, 46.8, 42.4, 35.3, 35.0, 33.6, 24.7, 23.7, 23.4, 22.9, 20.9, 11.9.

HRMS-APCI calculated for $C_{17}H_{27}$ $[M+H]^+$: 231.2113; found: 231.2111.

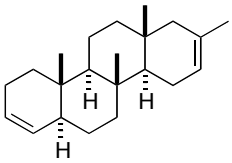


204

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 - 6.01 (m, 1H), 5.38 - 5.34 (m, 1H), 2.21 - 2.16 (m, 1H), 2.14 - 2.04 (m, 4H), 2.01 (m, 1H), 1.90 (m, 1H), 1.82 - 1.76 (m, 1H), 1.71 (dt, J = 13.3, 3.2 Hz, 1H), 1.64 (s, 3H), 1.56 (m, 1H), 1.47 (dd, J = 13.1, 3.1 Hz, 1H), 1.21 (m, 3H), 0.96 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.3, 128.3, 128.0, 119.9, 52.1, 51.4, 49.9, 42.1, 38.1, 34.6, 33.3, 25.2, 24.0, 23.7, 23.2, 20.8, 12.3.

HRMS-APCI calculated for $C_{17}H_{26}Br$ $[M+H]^+$: 309.1212; found: 309.1214.

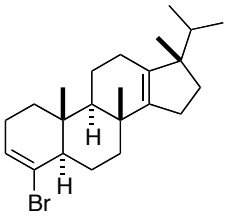


155

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (m, 1H), 5.34 (m, 2H), 2.09 (m, 2H), 2.02 - 1.74 (m, 6H), 1.73 - 1.61 (m, 6H), 1.51 - 1.32 (m, 4H), 1.26 - 1.16 (m, 2H), 1.13 - 1.06 (m, 1H), 1.05 - 0.93 (m, 4H), 0.93 - 0.83 (m, 4H), 0.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7, 131.2, 125.5, 119.9, 58.5, 53.5, 51.3, 46.4, 43.5, 40.6, 37.8, 35.5, 35.3, 33.2, 24.3, 23.7, 23.6, 22.7, 20.4, 17.8, 17.0, 12.3.

HRMS-APCI calculated for $C_{22}H_{35}$ $[M+H]^+$: 299.2733; found: 299.2730.

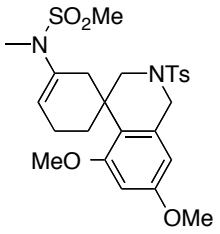


206

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (q, J = 3.6 Hz, 1H), 2.26 - 2.06 (m, 4H), 2.06 - 1.97 (m, 2H), 1.93 - 1.87 (m, 1H), 1.84 - 1.75 (m, 4H), 1.60 (m, 1H), 1.52 - 1.44 (m, 2H), 1.31 - 1.26 (m, 2H), 1.25 - 1.20 (m, 2H), 1.14 (m, 1H), 1.03 (s, 3H), 0.97 (s, 3H), 0.86 (s, 3H), 0.85 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.6, 128.0, 127.9, 53.8, 52.3, 51.7, 38.5, 38.0, 36.3, 34.6, 33.5, 30.2, 27.7, 25.3, 25.3, 24.3, 23.4, 20.8, 18.4, 18.2, 17.6, 12.5.

HRMS-ESI calculated for $C_{23}H_{35}BrNa$ $[M+Na]^+$: 413.1822; found: 413.1826.



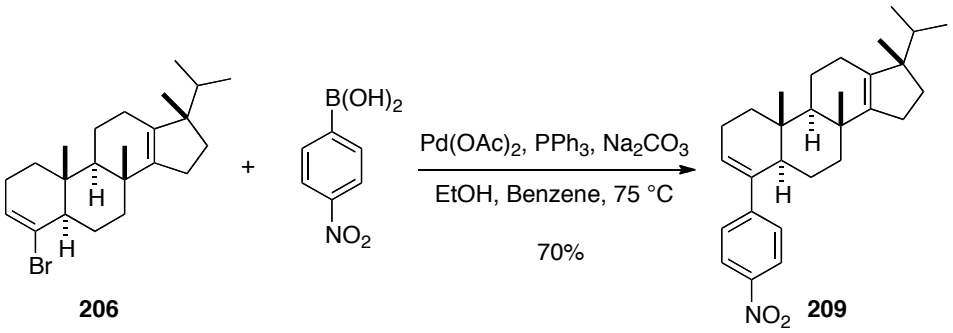
213

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.71 (m, 2H), 7.41 - 7.35 (m, 2H), 6.35 (d, J = 2.5 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 5.93 (d, J = 4.6 Hz, 1H), 4.31 - 4.21 (m, 1H), 3.92 (d, J = 14.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.41 - 3.33 (m, 1H), 3.15 (m, 1H), 3.11 (s, 3H), 2.96 (s, 3H), 2.73 (dd, J = 12.9, 9.1 Hz, 2H), 2.46 (s, 3H), 2.23 (t, J = 13.7 Hz, 3H), 1.45 - 1.37 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.9, 143.9, 137.5, 134.3, 132.6, 129.8, 127.8, 124.3, 121.3, 102.2, 98.6, 77.3, 77.2, 77.0, 76.7, 55.3, 55.2, 52.2, 49.9, 37.8, 37.2, 36.5, 33.7, 27.0, 21.7, 21.6.

HRMS-ESI calculated for $C_{25}H_{32}N_2NaO_6S_2$ $[M+Na]^+$: 543.1599; found: 543.1591.

(5*R,8*R**,9*R**,10*R**,17*S**)-17-isopropyl-8,10,17-trimethyl-4-(4-nitrophenyl)-2,5,6,7,8,9,10,11,12,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthrene (209)**



206 **209**

Degassed benzene (1.5 mL) and EtOH (0.5 mL) was added to a 10 ml microwave vial containing **206** (32 mg, 0.08 mmol), 4-nitrophenylboronic acid (20 mg, 0.12 mmol), PPh_3 (2.1 mg, 8 μmol), $Pd(OAc)_2$ (0.9 mg, 4

μmol) and Na_2CO_3 (17.4 mg, 0.16 mmol). The vial was purged with Argon and then fitted with a septa and vial seal. The reaction was then heated to 75 °C for 20 hours. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to give **209** (24.9 mg, 70%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.14 (m, 2H), 7.26 (d, J = 8.7 Hz, 2H), 5.62 (q, J = 3.4 Hz, 1H), 2.37 (dt, J = 12.7, 3.3 Hz, 1H), 2.31 – 2.22 (m, 3H), 2.12 – 2.02 (m, 2H), 2.02 – 1.93 (m, 1H), 1.87 (m, 1H), 1.83 – 1.76 (m, 2H), 1.71 – 1.65 (m, 1H), 1.64 – 1.60 (m, 1H), 1.42 – 1.37 (m, 2H), 1.27 – 1.15 (m, 5H), 1.01 (d, J = 0.6 Hz, 3H), 0.98 (s, 3H), 0.91 (d, J = 0.8 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 146.2, 143.7, 140.3, 137.6, 128.7, 127.7, 123.0, 54.0, 52.3, 48.2, 38.2, 36.2, 35.9, 34.7, 33.5, 30.2, 27.7, 25.3, 23.4, 23.3, 21.9, 20.9, 18.3, 18.2, 17.6, 12.6.

HRMS-ESI calculated for $C_{29}H_{39}NNaO_2$ $[M+Na]^+$: 456.2876; found: 456.2868.

Crystal data

Compound 175

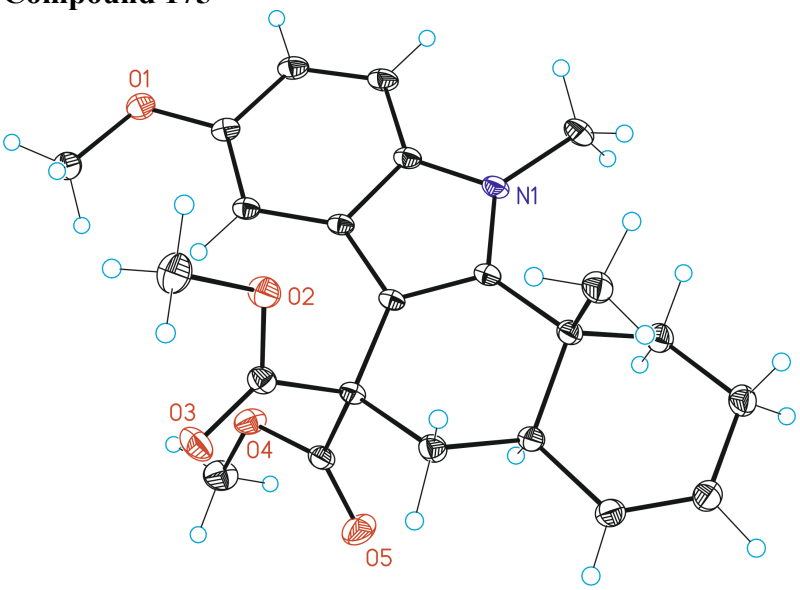


Table 1. Crystal data and structure refinement for mo_zrii7.

Identification code	mo_zrii7	
Empirical formula	C23 H27 N O5	
Formula weight	397.45	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.8767(14)Å	a= 90°.
	b = 23.638(3)Å	b = 102.363(4)°.
	c = 8.6175(12)Å	g = 90°.
Volume	1965.2(5) $Å^3$	
Z	4	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	848	
Crystal size	0.20 x 0.08 x 0.04 mm^3	
Theta range for data collection	1.723 to 33.188°.	
Index ranges	-15<=h<=15,-36<=k<=36,-13<=l<=12	
Reflections collected	59094	
Independent reflections	7505[R(int) = 0.0271]	
Completeness to theta =33.188°	99.8%	
Absorption correction	Empirical	
Max. and min. transmission	0.996 and 0.766	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7505/ 0/ 267	
Goodness-of-fit on F^2	1.127	

Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1255
R indices (all data)	R1 = 0.0530, wR2 = 0.1284
Largest diff. peak and hole	0.629 and -0.338 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for mo_zrii7.

Bond lengths----	
N1-C1	1.3850(13)
N1-C16	1.3877(12)
N1-C17	1.4571(13)
O1-C4	1.3748(12)
O1-C18	1.4229(13)
O2-C21	1.3338(12)
O2-C22	1.4460(13)
O3-C21	1.2098(12)
O4-C19	1.3390(12)
O4-C20	1.4461(13)
O5-C19	1.2037(12)
C1-C2	1.4012(13)
C1-C6	1.4110(13)
C2-C3	1.3786(15)
C3-C4	1.4110(14)
C4-C5	1.3862(13)
C5-C6	1.4121(13)
C6-C7	1.4361(12)
C7-C16	1.3841(13)
C7-C8	1.5127(12)
C8-C21	1.5279(13)
C8-C19	1.5390(13)
C8-C9	1.5490(13)
C9-C10	1.5252(14)
C10-C11	1.5066(14)

C10-C15	1.5491(13)
C11-C12	1.3343(14)
C12-C13	1.4994(15)
C13-C14	1.5340(15)
C14-C15	1.5469(14)
C15-C16	1.5104(13)
C15-C23	1.5485(14)

Angles----------

C1-N1-C16	108.44(8)
C1-N1-C17	122.56(8)
C16-N1-C17	129.00(9)
C4-O1-C18	116.95(8)
C21-O2-C22	114.88(8)
C19-O4-C20	115.16(8)
N1-C1-C2	129.34(9)
N1-C1-C6	108.72(8)
C2-C1-C6	121.93(9)
C3-C2-C1	117.57(9)
C2-C3-C4	121.34(9)
O1-C4-C5	124.60(9)
O1-C4-C3	113.94(8)
C5-C4-C3	121.46(9)
C4-C5-C6	117.99(8)
C1-C6-C5	119.67(8)
C1-C6-C7	106.16(8)
C5-C6-C7	134.15(8)
C16-C7-C6	107.67(8)
C16-C7-C8	123.98(8)
C6-C7-C8	128.29(8)
C7-C8-C21	113.76(7)
C7-C8-C19	110.59(7)

C21-C8-C19	107.39(7)
C7-C8-C9	110.43(7)
C21-C8-C9	105.34(7)
C19-C8-C9	109.10(7)
C10-C9-C8	110.29(8)
C11-C10-C9	113.31(8)
C11-C10-C15	112.27(8)
C9-C10-C15	112.36(8)
C12-C11-C10	122.24(9)
C11-C12-C13	122.75(9)
C12-C13-C14	113.29(8)
C13-C14-C15	111.47(8)
C16-C15-C14	115.17(8)
C16-C15-C23	107.98(8)
C14-C15-C23	110.55(8)
C16-C15-C10	105.61(7)
C14-C15-C10	105.58(7)
C23-C15-C10	111.89(8)
C7-C16-N1	108.99(8)
C7-C16-C15	124.70(8)
N1-C16-C15	125.98(8)
O5-C19-O4	123.32(9)
O5-C19-C8	124.67(9)
O4-C19-C8	112.00(8)
O3-C21-O2	124.11(9)
O3-C21-C8	123.35(9)
O2-C21-C8	112.39(8)

Table 3. Torsion angles [°] for mo_zrii7.

C16-N1-C1-C2	-179.11(10)

C17-N1-C1-C2	1.55(16)
C16-N1-C1-C6	1.19(10)
C17-N1-C1-C6	-178.15(9)
N1-C1-C2-C3	-178.90(9)
C6-C1-C2-C3	0.77(14)
C1-C2-C3-C4	0.88(15)
C18-O1-C4-C5	0.30(14)
C18-O1-C4-C3	-179.68(9)
C2-C3-C4-O1	178.84(9)
C2-C3-C4-C5	-1.14(15)
O1-C4-C5-C6	179.75(9)
C3-C4-C5-C6	-0.27(14)
N1-C1-C6-C5	177.55(8)
C2-C1-C6-C5	-2.18(14)
N1-C1-C6-C7	-1.04(10)
C2-C1-C6-C7	179.23(9)
C4-C5-C6-C1	1.87(13)
C4-C5-C6-C7	179.99(9)
C1-C6-C7-C16	0.51(10)
C5-C6-C7-C16	-177.79(10)
C1-C6-C7-C8	177.88(9)
C5-C6-C7-C8	-0.42(17)
C16-C7-C8-C21	129.70(9)
C6-C7-C8-C21	-47.28(12)
C16-C7-C8-C19	-109.36(10)
C6-C7-C8-C19	73.66(11)
C16-C7-C8-C9	11.50(12)
C6-C7-C8-C9	-165.47(9)
C7-C8-C9-C10	-40.96(10)
C21-C8-C9-C10	-164.20(8)
C19-C8-C9-C10	80.78(9)
C8-C9-C10-C11	-164.69(8)

C8-C9-C10-C15	66.75(10)
C9-C10-C11-C12	-155.31(10)
C15-C10-C11-C12	-26.70(13)
C10-C11-C12-C13	4.21(16)
C11-C12-C13-C14	-12.11(14)
C12-C13-C14-C15	42.71(11)
C13-C14-C15-C16	-179.11(8)
C13-C14-C15-C23	58.16(10)
C13-C14-C15-C10	-63.03(10)
C11-C10-C15-C16	176.39(8)
C9-C10-C15-C16	-54.50(10)
C11-C10-C15-C14	53.95(10)
C9-C10-C15-C14	-176.94(8)
C11-C10-C15-C23	-66.37(10)
C9-C10-C15-C23	62.74(10)
C6-C7-C16-N1	0.21(10)
C8-C7-C16-N1	-177.31(8)
C6-C7-C16-C15	174.01(8)
C8-C7-C16-C15	-3.50(14)
C1-N1-C16-C7	-0.86(11)
C17-N1-C16-C7	178.42(10)
C1-N1-C16-C15	-174.57(8)
C17-N1-C16-C15	4.72(16)
C14-C15-C16-C7	139.83(9)
C23-C15-C16-C7	-96.09(10)
C10-C15-C16-C7	23.75(12)
C14-C15-C16-N1	-47.42(13)
C23-C15-C16-N1	76.66(11)
C10-C15-C16-N1	-163.49(9)
C20-O4-C19-O5	2.32(15)
C20-O4-C19-C8	-178.55(9)
C7-C8-C19-O5	112.58(11)

C21-C8-C19-O5	-122.77(11)
C9-C8-C19-O5	-9.07(14)
C7-C8-C19-O4	-66.53(10)
C21-C8-C19-O4	58.12(10)
C9-C8-C19-O4	171.82(8)
C22-O2-C21-O3	-2.27(14)
C22-O2-C21-C8	-177.90(8)
C7-C8-C21-O3	152.50(9)
C19-C8-C21-O3	29.79(12)
C9-C8-C21-O3	-86.41(11)
C7-C8-C21-O2	-31.83(11)
C19-C8-C21-O2	-154.55(8)
C9-C8-C21-O2	89.26(9)

Compound 183

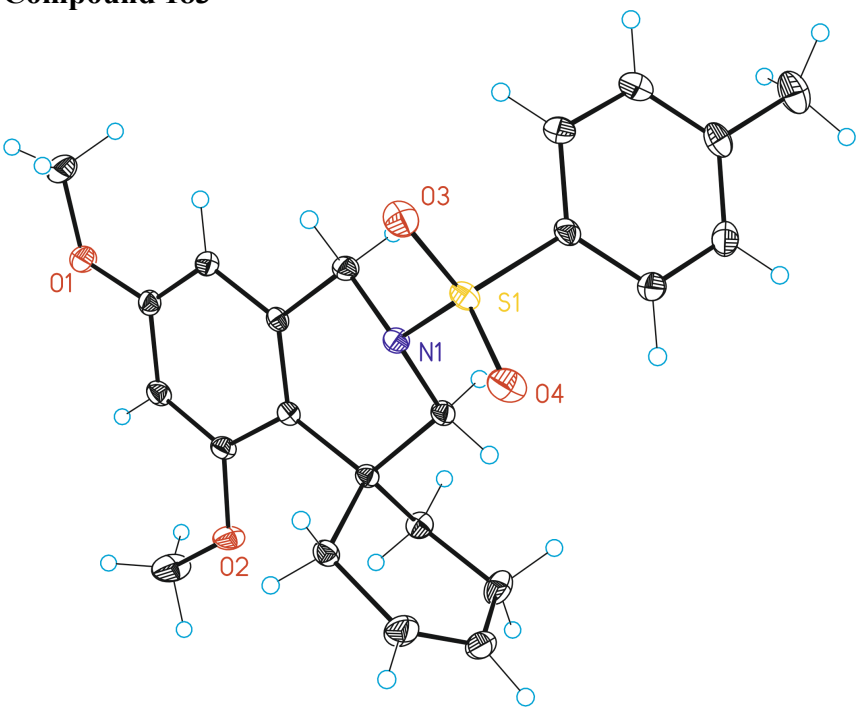


Table 1. Crystal data and structure refinement for mo_zri185_0m.

Identification code	mo_zri185_0m
Empirical formula	C23 H27 N O4 S
Formula weight	413.51
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 9.4223(6)Å a= 90°.
	b = 20.6490(13)Å b = 105.9641(19)°.
	c = 10.9082(8)Å g = 90°.
Volume	2040.5(2) $Å^3$
Z	4
Density (calculated)	1.346 Mg/m^3
Absorption coefficient	0.189 mm^{-1}
F(000)	880
Crystal size	0.35 x 0.35 x 0.30 mm^3
Theta range for data collection	1.972 to 32.427°.
Index ranges	-13<=h<=8,-15<=k<=31,-14<=l<=16
Reflections collected	14366
Independent reflections	6481[R(int) = 0.0237]
Completeness to theta =32.427°	88.0%
Absorption correction	Empirical
Max. and min. transmission	0.946 and 0.885
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6481/ 0/ 269
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.1059
R indices (all data)	R1 = 0.0510, wR2 = 0.1111

Largest diff. peak and hole	0.428 and -0.493 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for mo_zri185_0m.

Bond lengths----	
S1-O4	1.4318(10)
S1-O3	1.4357(9)
S1-N1	1.6377(10)
S1-C17	1.7598(12)
N1-C8	1.4650(15)
N1-C7	1.4685(14)
O1-C11	1.3588(14)
O1-C15	1.4224(16)
O2-C13	1.3713(14)
O2-C16	1.4245(15)
C1-C14	1.5264(15)
C1-C7	1.5397(15)
C1-C2	1.5453(16)
C1-C6	1.5453(16)
C2-C3	1.5007(18)
C3-C4	1.3664(19)
C4-C5	1.4554(19)
C5-C6	1.5166(17)
C8-C9	1.5117(15)
C9-C14	1.3960(15)
C9-C10	1.3994(16)
C10-C11	1.3832(16)
C11-C12	1.3965(16)
C12-C13	1.3802(16)
C13-C14	1.4213(15)
C17-C18	1.3919(17)
C17-C22	1.3938(16)

C18-C19	1.3875(18)
C19-C20	1.3952(19)
C20-C21	1.3936(19)
C20-C23	1.5065(19)
C21-C22	1.3859(18)

Angles----------

O4-S1-O3	119.61(6)
O4-S1-N1	106.97(5)
O3-S1-N1	106.90(5)
O4-S1-C17	107.64(6)
O3-S1-C17	108.29(6)
N1-S1-C17	106.78(5)
C8-N1-C7	110.10(9)
C8-N1-S1	116.60(7)
C7-N1-S1	116.84(8)
C11-O1-C15	116.82(10)
C13-O2-C16	117.33(10)
C14-C1-C7	109.36(9)
C14-C1-C2	110.41(9)
C7-C1-C2	109.00(9)
C14-C1-C6	112.69(9)
C7-C1-C6	105.86(9)
C2-C1-C6	109.37(9)
C3-C2-C1	112.93(10)
C4-C3-C2	121.84(12)
C3-C4-C5	123.30(12)
C4-C5-C6	115.43(11)
C5-C6-C1	111.92(10)
N1-C7-C1	110.68(9)
N1-C8-C9	109.63(9)
C14-C9-C10	122.90(10)

C14-C9-C8	121.78(10)
C10-C9-C8	115.32(9)
C11-C10-C9	118.99(10)
O1-C11-C10	125.26(11)
O1-C11-C12	114.52(10)
C10-C11-C12	120.21(11)
C13-C12-C11	119.91(10)
O2-C13-C12	121.53(10)
O2-C13-C14	116.58(10)
C12-C13-C14	121.88(10)
C9-C14-C13	115.99(10)
C9-C14-C1	121.90(10)
C13-C14-C1	122.07(10)
C18-C17-C22	120.40(11)
C18-C17-S1	119.29(9)
C22-C17-S1	120.25(9)
C19-C18-C17	119.39(11)
C18-C19-C20	121.20(12)
C21-C20-C19	118.34(12)
C21-C20-C23	120.33(12)
C19-C20-C23	121.33(13)
C22-C21-C20	121.40(12)
C21-C22-C17	119.26(12)

Table 3. Torsion angles [°] for mo_zri185_0m.

O4-S1-N1-C8	176.01(8)
O3-S1-N1-C8	46.78(10)
C17-S1-N1-C8	-68.96(9)
O4-S1-N1-C7	-50.82(10)
O3-S1-N1-C7	179.95(8)

C17-S1-N1-C7	64.21(9)
C14-C1-C2-C3	171.69(10)
C7-C1-C2-C3	-68.16(12)
C6-C1-C2-C3	47.14(13)
C1-C2-C3-C4	-20.97(18)
C2-C3-C4-C5	2.2(2)
C3-C4-C5-C6	-11.62(18)
C4-C5-C6-C1	39.40(15)
C14-C1-C6-C5	179.88(10)
C7-C1-C6-C5	60.39(12)
C2-C1-C6-C5	-56.91(13)
C8-N1-C7-C1	-70.83(12)
S1-N1-C7-C1	153.15(8)
C14-C1-C7-N1	45.99(12)
C2-C1-C7-N1	-74.81(11)
C6-C1-C7-N1	167.64(9)
C7-N1-C8-C9	55.82(12)
S1-N1-C8-C9	-168.05(8)
N1-C8-C9-C14	-22.40(15)
N1-C8-C9-C10	158.67(10)
C14-C9-C10-C11	-1.13(17)
C8-C9-C10-C11	177.78(10)
C15-O1-C11-C10	-6.79(18)
C15-O1-C11-C12	171.95(12)
C9-C10-C11-O1	179.97(11)
C9-C10-C11-C12	1.29(17)
O1-C11-C12-C13	-177.64(11)
C10-C11-C12-C13	1.17(18)
C16-O2-C13-C12	5.34(18)
C16-O2-C13-C14	-176.30(12)
C11-C12-C13-O2	174.37(11)
C11-C12-C13-C14	-3.91(18)

C10-C9-C14-C13	-1.41(17)
C8-C9-C14-C13	179.74(10)
C10-C9-C14-C1	-179.23(10)
C8-C9-C14-C1	1.93(17)
O2-C13-C14-C9	-174.41(10)
C12-C13-C14-C9	3.95(17)
O2-C13-C14-C1	3.40(17)
C12-C13-C14-C1	-178.24(11)
C7-C1-C14-C9	-13.22(15)
C2-C1-C14-C9	106.71(12)
C6-C1-C14-C9	-130.66(11)
C7-C1-C14-C13	169.10(10)
C2-C1-C14-C13	-70.97(13)
C6-C1-C14-C13	51.66(14)
O4-S1-C17-C18	28.37(11)
O3-S1-C17-C18	159.00(10)
N1-S1-C17-C18	-86.20(10)
O4-S1-C17-C22	-154.36(10)
O3-S1-C17-C22	-23.73(11)
N1-S1-C17-C22	91.07(10)
C22-C17-C18-C19	0.08(18)
S1-C17-C18-C19	177.35(10)
C17-C18-C19-C20	0.46(19)
C18-C19-C20-C21	-0.25(19)
C18-C19-C20-C23	-179.94(12)
C19-C20-C21-C22	-0.51(19)
C23-C20-C21-C22	179.18(12)
C20-C21-C22-C17	1.04(19)
C18-C17-C22-C21	-0.82(18)
S1-C17-C22-C21	-178.06(9)

Chapter 2. Studies on the Asymmetric Gold(I)-Catalyzed Polycyclization

Background

The development of enantioselective catalytic process involving gold(I) is an important challenge in homogeneous catalysis. The dearth of the enantioselective gold(I)-catalyzed transformations can be traced to the propensity of gold(I) to form linear two-coordinate complexes,[55] in which the reacting substrate is positioned far from the potential source of ligand-centered chirality. The problems associated with ligand/substrate proximity are further exacerbated by the out-sphere nature of π–activation catalysis that bypasses nucleophile-metal interaction prior to C−X bond formation.[56]

In despite of this challenge, much of the progress in the enantioselective synthesis enabled by gold catalysis has been achieved in the last few years.[57] In early 2005, our group reported the gold(I)-catalyzed enantioselective alkoxycyclization of 1,6-enynes to form methylenecyclopentanes.[58] These transformations represented both the first examples of enantioselective gold(I) catalysis involving π-activation and the first successful application of chiral bis(gold) complexes in enantioselective catalysis. For example, a 1.6:2 mixture of [{(*R*)-tol-binap}$(AuCl)_2$] (**239**) and $AgSbF_6$ catalyzed the alkoxycyclization of enyne **240a** with methanol (10 equiv) at room temperature for 4 h to form methylenecyclopentane **241a** in 89% yield with 53% enantiomeric excess (Scheme 53). In comparison, phenyl-substituted enyne **240b** underwent

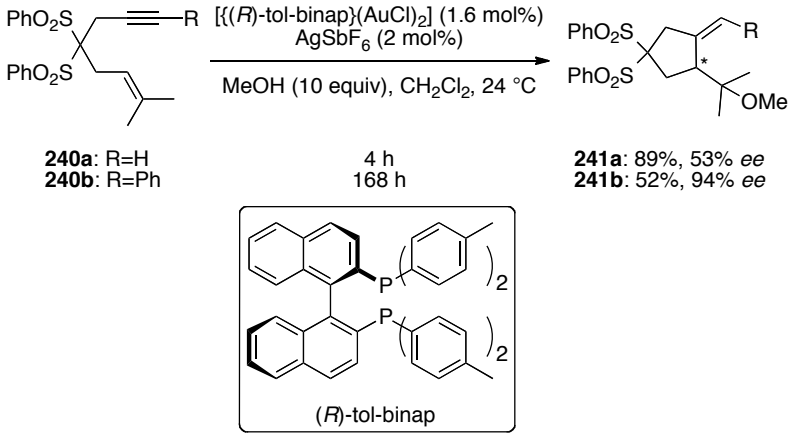
55 (a) Gimeno, M. C.; Laguna, A. *Chem. Rev*. **1997**, *97*, 511−522. (b) Carvajal, M. A.; Novoa, J. J.; Alvarez, S. *J. Am. Chem. Soc*. **2004**, *126*, 1465−1477. (c) Schwerdtfeger, P.; Hermann, H. L.; Schmidbaur, H. *Inorg. Chem*. **2003**, *42*, 1334−1342.

56 (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc*. **2004**, *126*, 4526−4527. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc*. **2006**, *128*, 1798−1799. (c) Hashimi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391–4394. (d) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412.

57 Recent reviews on asymmetric gold catalysis: (a) Widenhoefer, R. A. *Chem. Eur. J*. **2008**, *14*, 5382−5391. (b) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609−619. (c) Pradal, P.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 1501−1514. (d) Zi, W.; Toste, F. D. *Chem. Soc. Rev*. **2016**, *45*, 4567−4589. (e) Li, Y.; Li, W.; Zhang, J. *Chem. Eur. J*. **2017**, *23*, 467−512.

58 Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293−1330.

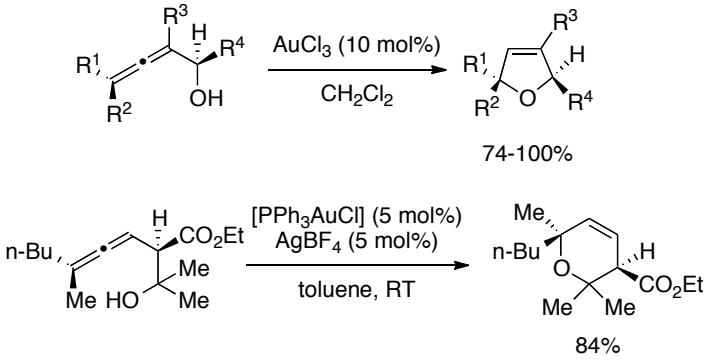
slow alkoxycyclization to form **241b** with high enantioselectivity, but modest yield. The first gold(I)-catalyzed enantioselective polycyclization was reported by Toste in 2010 which has been mentioned in general introduction.[35]



Scheme 53. Enantioselective Alkoxycyclization of 1,6-Enynes

Alternatively, asymmetric induction through chirality transfer is a solution to asymmetric gold catalysis. In one of the earliest works highlighting chirality transfer from the substrates to the product, Krause and co-workers reported the *endo*-cycloisomerization of both α- and β-hydroxyallenes with both gold(I) and gold(III) chloride salts (Scheme 54).[59] These reactions represent a mild and efficient method for the synthesis of dihydrofuran and tetrahydropyran derivatives with complete axis-to-center chirality transfer. Both reactions offer a large substrate scope and the products were obtained in good to excellent yields.

59 (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537–2538. (b) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759−1774. (c) Krause, N.; Gockel, B. *Org. Lett.* **2006**, *8*, 4485–4488. (d) Deutsch, C.; Gockel, B.; Hoffmann-Röder, A.; Krause, N. *Synlett* **2007**, 1790−1794.



Scheme 54. Gold-Catalyzed Cycloisomerization of Allenyl Carbinols with Axis-to-Center Chirality Transfer

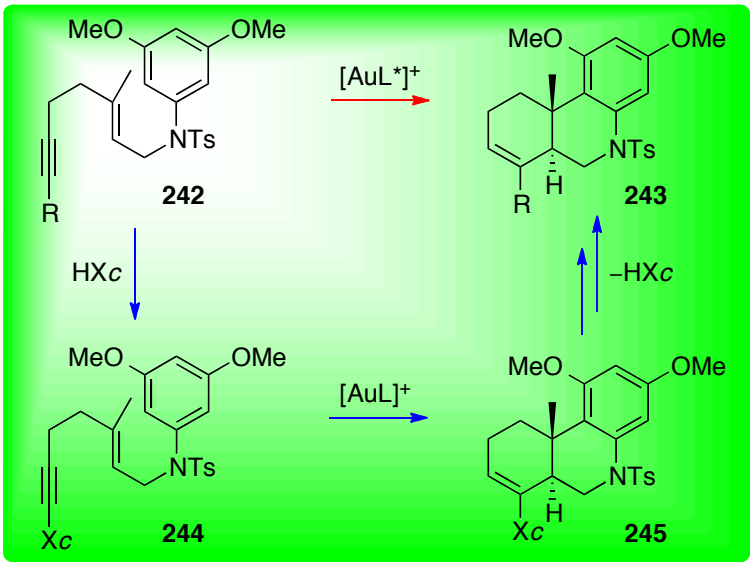
The drawback of asymmetric induction through chirality transfer compared to enantioselective catalysis is that an enantioenriched substrate is required for the transformation and the transformation usually applies only for some specific substrates.

Objectives

Obtaining enantioenriched polycycles through gold(I)-catalyzed polycyclization of 1,5-enynes is of much synthetic significance. The discovery of suitable conditions, especially a chiral ligand that generally fits the transformation is quite challenging.

While asymmetric induction through chirality transfer requires enantioenriched substrates, an alternative is the use of a chiral auxiliary to achieve asymmetric synthesis. We postulated that a chiral auxiliary located next to the alkynyl group could control the diastereoselectivity during the gold(I)-catalyzed polycyclization of 1,5-enynes. Thus, the readily introduced and removed chiral auxiliary would be a good solution to the asymmetric synthesis of polycycles since it avoids the requirement of the use of enantioenriched 1,5-enynes.

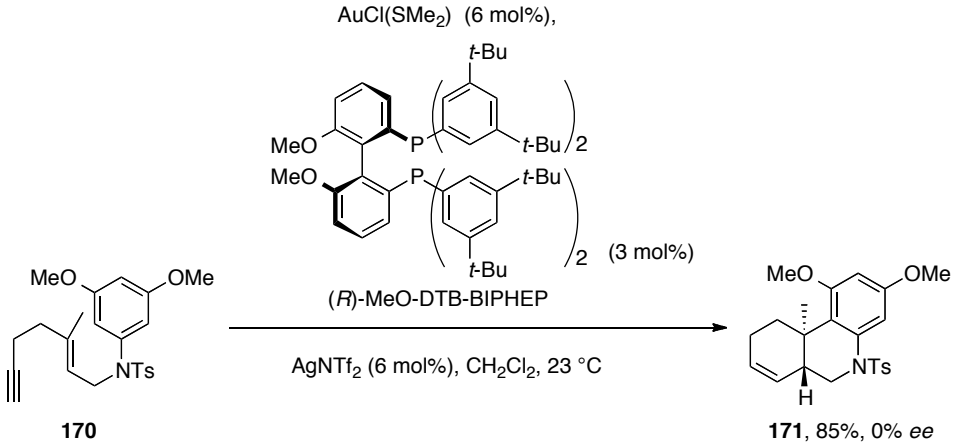
Specifically, achiral substrate **242** could be converted to **243** enantioselectively by a chiral gold(I) complex. Alternatively, a chiral auxiliary (HX*c*) can be introduced to form **244** which can be converted to **245** diastereoselectively with an achiral gold(I) catalyst. Then, the chiral auxiliary can be removed to give enantioenriched product **243** (Scheme 55).



Scheme 55. Two Strategies for the Formation of Enantioenriched 243

Results and Discussions

We chose 1,5-enyne **170** to expolre the conditions for the enantioselective synthesis of polycycles. To facilitate the process of condition screening, a protocol that generates the cationic gold(I) catalyst *in situ* was applied. For example, chloro(dimethylsulfide)gold(I) (6 mol%) and (*R*)-MeO-DTB-BIPHEP (3 mol%) were mixed in CH_2Cl_2 to generate the precatalyst (*R*)-MeO-DTB-BIPHEP$(AuCl)_2$ which upon treatment of $AgSbF_6$ (6 mol%), generated the active cationic gold(I) species in situ. Then a solution of **170** in CH_2Cl_2 was added, leading to the formation of **171** without any decrease in yield (85%) compared to the protocol used previously, although this product was obtained as a racemic mixture (Scheme 56).

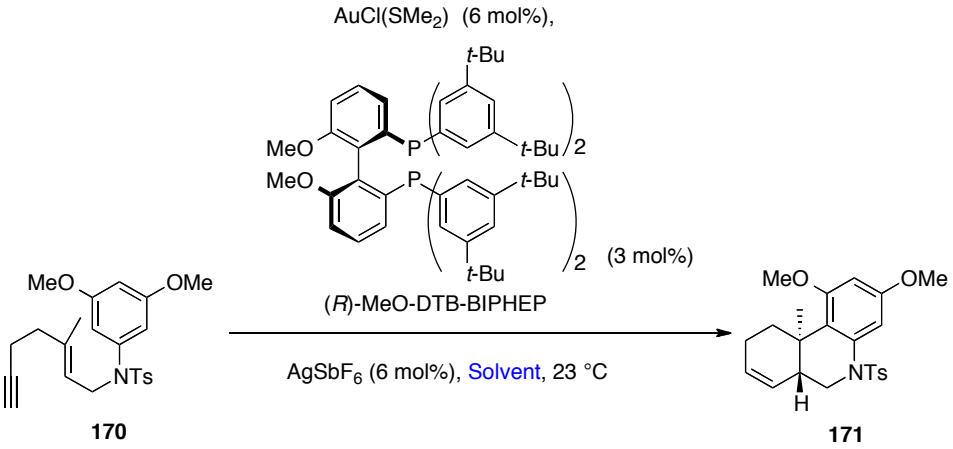


170 **171**, 85%, 0% *ee*

Scheme 56

We first examined the influence of solvent on the enantioselectivity. Different commonly used solvents were employed in the protocol decribed above. No enantioselectivity was obtained with solvents such as dichloromethane and acetonitrile (Table 11, entries 1 and 4). Ethyl ether and tetrahydrofuran gave the product with *ca.* 20% *ee* (Table 11, entries 2 and 3). The best *ee* (around 30-35%) were obtained in aromatic solvents such as toluene and *m*-xylene (Table 11, entries 7-9).

Table 11. The Influence of Solvent on Gold(I)-Catalyzed Enantioselective Cyclization of 170[a]



170 **171**

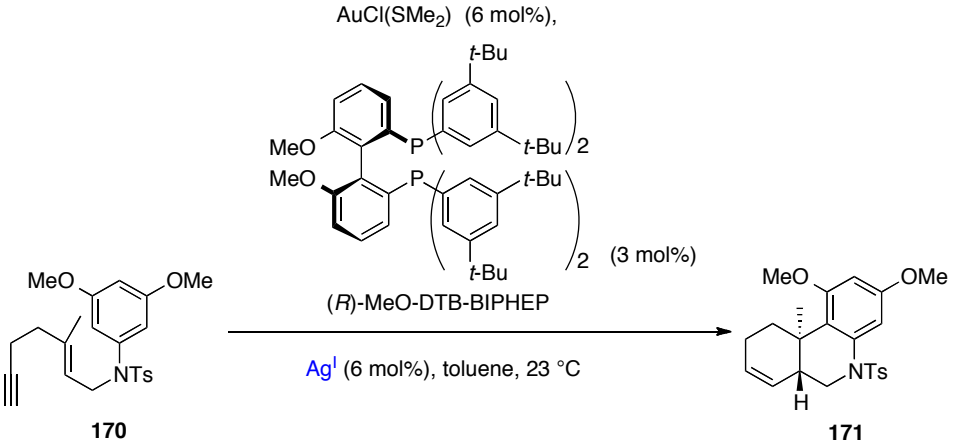
Entry	Solvent	*ee* (%)[b]
1	CH_2Cl_2	0
2	Et_2O	18
3	THF	21
4	CH_3CN	0
5	CH_3NO_2	10
6	Benzene	6
7	Toluene	35
8[c]	Toluene	33
9	*m*-Xylene	31

[a] Reactions carried out with $AuCl(SMe_2)$ (6 mol%), (*R*)-MeO-DTB-BIPHEP (3 mol%) and $AgSbF_6$ (6 mol%) in solvent (0.05 M) at 23 °C for 1 h. [b] Enantiomeric excess was determined by HPLC analysis. Abolute configuration of the major enantiomer was not confirmed. [c] 3 mol% of $AgSbF_6$ was used.

The counterion of the cationic gold(I) catalyst could also play an important role in enantioselective transformations. We therefore screened different silver(I) salts in this reaction. All reactions furnished **171** in

excellent yields, although the use of NaBARF slowed down the reaction. It was found that $AgNTf_2$ outperformed other silver salts to give **171** in 54% ee (Table 12, entry 5).

Table 12. The Counterion Effect on Gold(I)-Catalyzed Enantioselective Cyclization of 170[a]



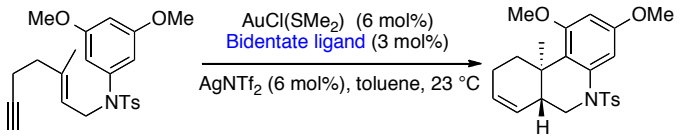
Entry	Ag^I	*ee* (%)[b]
1	$AgSbF_6$	35
2	AgOTf	18
3	$AgBF_4$	<5
4	$AgPF_6$	<5
5	$AgNTf_2$	54
6	NaBARF[c]	20

[a] Reactions carried out with $AuCl(SMe_2)$ (6 mol%), (*R*)-MeO-DTB-BIPHEP (3 mol%) and Ag^I (6 mol%) in toluene (0.05 M) at 23 °C for 1 h. [b] Enantiomeric excess was determined by HPLC analysis. Abolute configuration of the major enantiomer was not confirmed. [c] NaBARF=sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate.

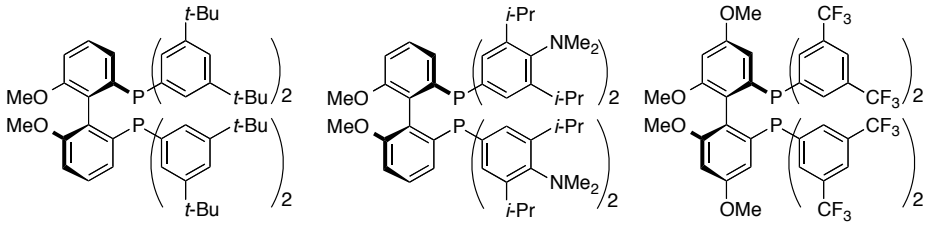
After solvent and silver salt screening, we then screened different ligands. First, we examined bidentate ligands **246-265**. Complexes of biphenylphosphines **246-250** bearing bulky aromatic rings gave **171** in

22-54% *ee*. Other bidentate phosphine ligands **251**-**262** gave **171** in <10% *ee*. Nitrogen-containing ligands (**247**, **252**, **255** and **263**) resulted in low conversions since gold(I) complexes are Lewis acidic and can coordinate with the basic centers of these ligands. Phosphite ligands **264** and **265** also furnished **171** in low enantiomeric excess (Table 13).

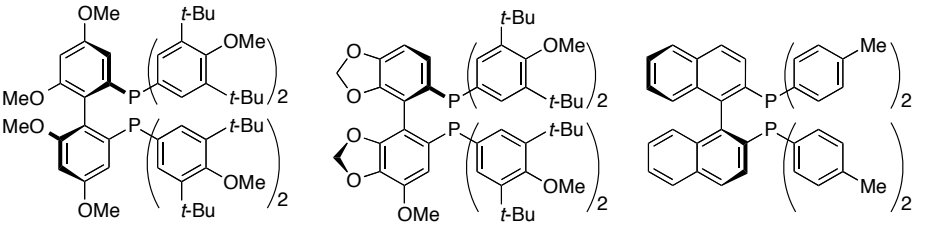
Table 13. The Screening of Bidentate Ligands for Enantioselective Cyclization of 170[a,b]



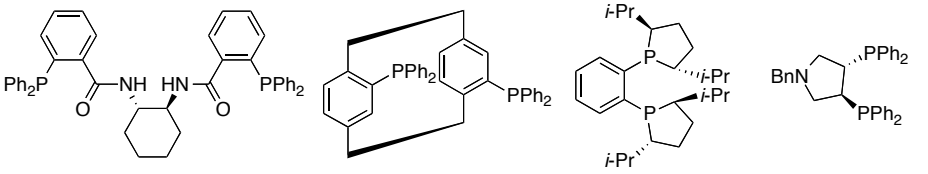
170 **171**



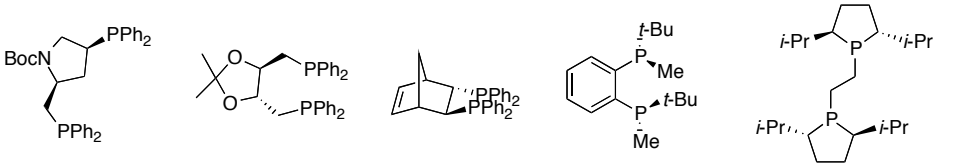
246, 54% *ee* **247**, 38% *ee*, low conversion **248**, 22% *ee*



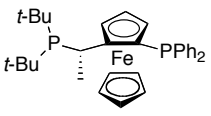
249, 27% *ee* **250**, 31% *ee* **251**, <5% *ee*



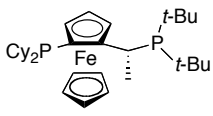
252, 5% *ee*, low conversion **253**, 9% *ee* **254**, <5% *ee* **255**, no reaction



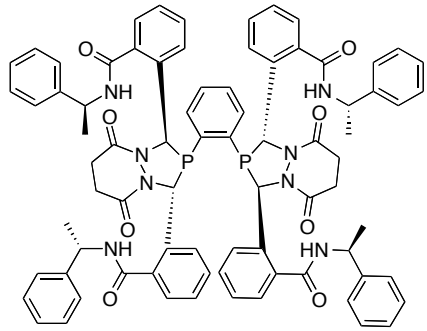
256, 9% *ee* **257**, no reaction **258**, 0% *ee* **259**, 0% *ee* **260**, <5% *ee*



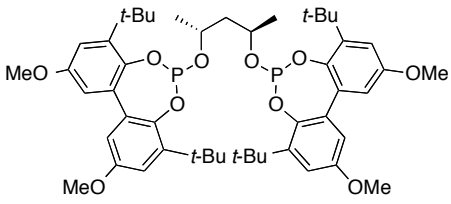
261, 13% *ee*



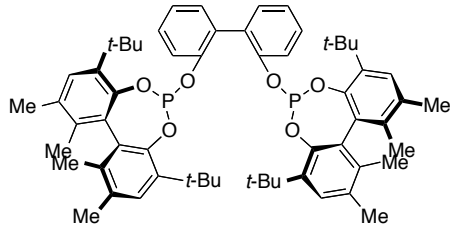
262, 5% *ee*



263, 6% *ee*, low conversion



264, 11% *ee*

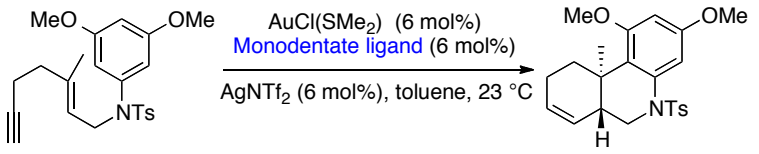


265, 7% *ee*

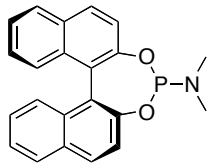
[a] Reactions carried out with $AuCl(SMe_2)$ (6 mol%), bidentate ligand (3 mol%) and $AgNTf_2$ (6 mol%) in toluene (0.05 M) at 23 °C for 1 h.
[b] Enantiomeric excess was determined by HPLC analysis. Abolute configuration of the major enantiomer was not confirmed.

We also tested some monodentate ligands for the polycyclization of 1,5-enyne **170**. It was found that these monodentate ligands provided **171** in low enantiomeric excess (Table 14).

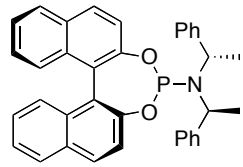
Table 14. The Screening of Monodentate Ligands for Enantioselective Cyclization of 170[a,b]



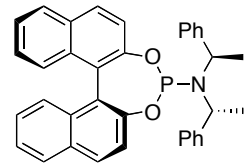
170 **171**



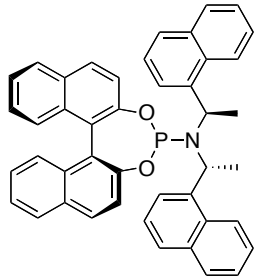
266, 0% *ee*



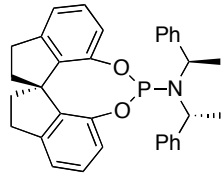
267, 16% *ee*



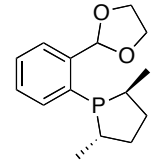
268, 12% *ee*



269, 6% *ee*



270, 7% *ee*

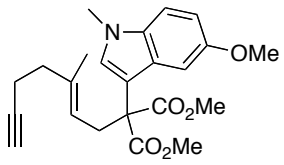
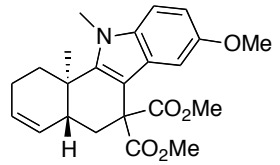
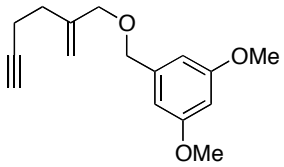
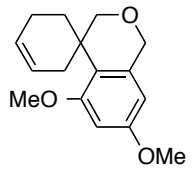
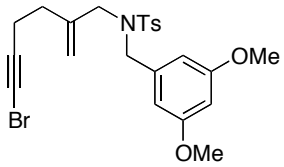
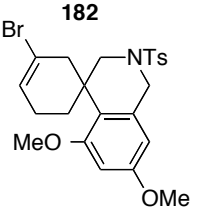


271, 9% *ee*

[a] Reactions carried out with $AuCl(SMe_2)$ (6 mol%), monodentate ligand (6 mol%) and $AgNTf_2$ (6 mol%) in toluene (0.05 M) at 23 °C for 1 h.
[b] Enantiomeric excess was determined by HPLC analysis. Abolute configuration of the major enantiomer was not confirmed.

Other attempts, such as lowering reaction temperature and lowering catalyst loadings did not help improving the enantioselectivity. We then applied the best conditions to other substrates. However, unfortunately compounds **174**, **180** and **197** did not give satisfactory enantiomeric excess (Table 15).

Table 15. Gold(I)-Catalyzed Enantioselective Cyclization of 174, 180 and 197[a]

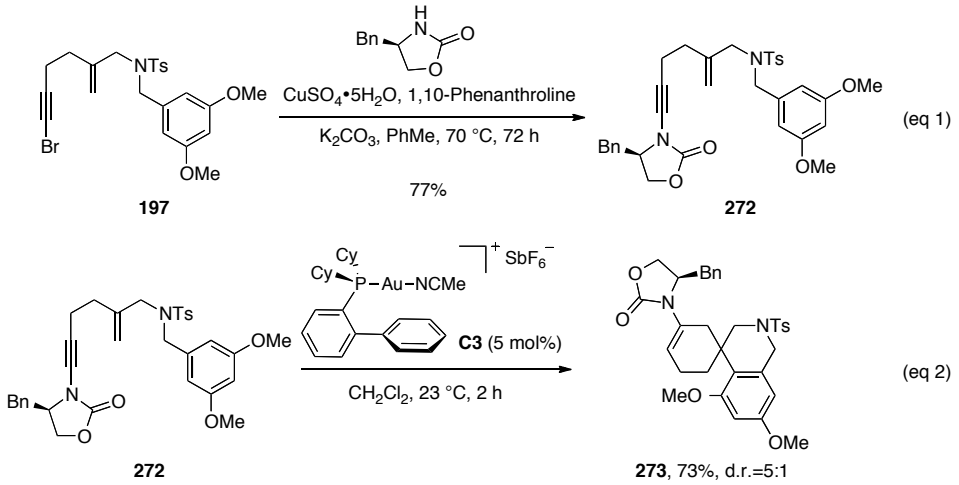
Entry	Substrate	Product[b]	Yield, *ee* (%)[c]
1	 **174**	 **175**	95, 48
2	 **180**	 **182**	79, 5
3	 **197**	 **198**	85, 18

[a] Reactions carried out with $AuCl(SMe_2)$ (6 mol%), **246** (3 mol%) and $AgNTf_2$ (6 mol%) in toluene (0.05 M) at 23 °C for 1 h.
[b] Abolute configuration of the major enantiomer was not confirmed.
[c] Enantiomeric excess was determined by HPLC analysis.

Since the attempts to develop a general enantioselective catalytic cyclization were not successful, we then turned our attention to the chiral auxiliary enabled asymmetric catalysis. Oxazolidinone auxiliaries, popularized by David Evans in aldol reactions,[60] alkylation reactions[61] and Diels-Alder reactions,[62] were examined first. These auxiliaries can be readily installed by a copper-catalyzed cross-coupling reaction with

60 Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127−2129.
61 Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737−1739.
62 (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc*. **1984**, *106*, 4261−4263. (b) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed*. **1987**, *26*, 1184−1186.

bromoalkynes. For instance, bromoalkyne **197** underwent a copper-catalyzed cross-coupling reaction with (*R*)-4-benzyl-2-oxazolidinone to form **272** in 77% yield (Scheme 57, eq 1). Then, **272** was exposed to 5 mol% of **C3** in CH_2Cl_2 at 23 °C for 2 h, giving spirocyclized product **273** in 73% yield with 5:1 diastereomeric ratio (Scheme 57, eq 2). The configuration of each diastereomer was not determined. It is noteworthy that this is the first gold(I)-catalyzed asymmetric synthesis enabled by a chiral oxazolidinone auxiliary.



Scheme 57

We also considered the potential use of chiral camphorsultam auxiliary that has been used in Michael additions,[63] asymmetric Claisen rearrangement[64] and total synthesis of Manzacidin B.[65]

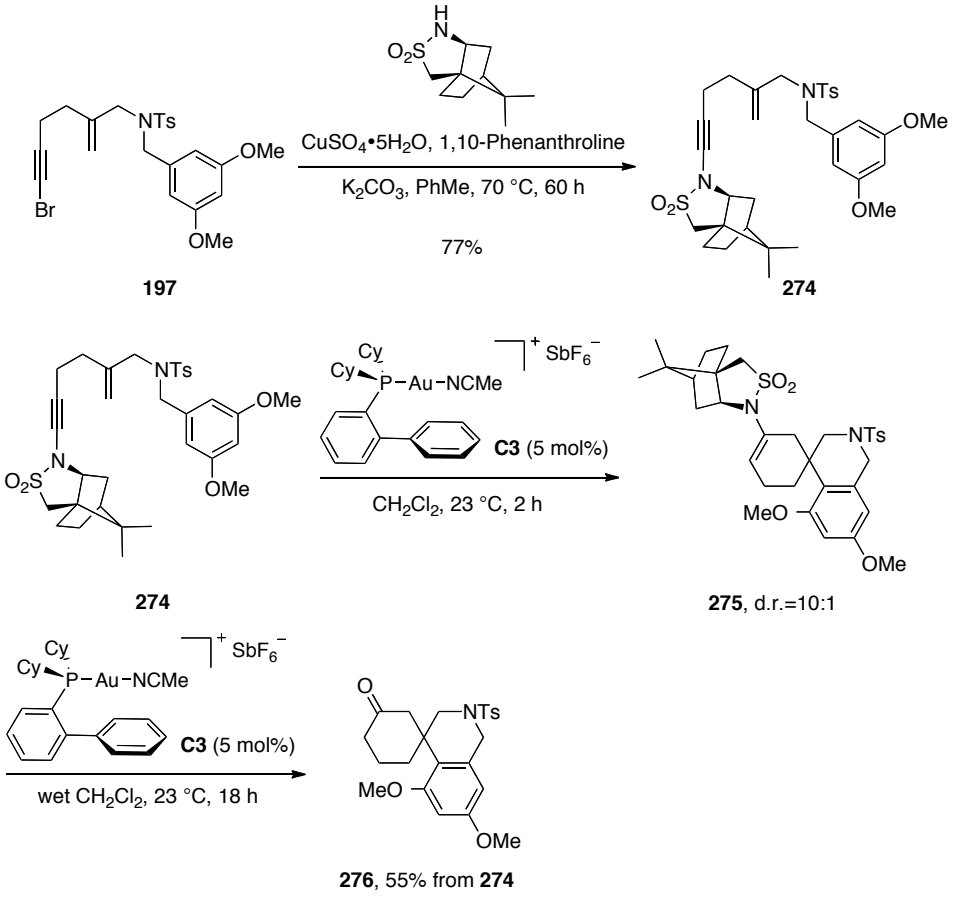
However, there was no report on chiral camphorsultam auxiliary enabled asymmetric gold catalysis. The auxiliary can be installed by the same method as the oxazolidinone auxiliary to the terminal position of an alkyne. For instance, bromoalkyne **197** underwent cross-coupling reaction with commercial available (1*R*)-(+)-2,10-camphorsultam to give **274** in 77% yield. Sultam **274** was then submitted to the same conditions as **272**

63 Tsai, W.-J.; Lin, Y.-T.; Uang, B.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1195−1198.

64 Takao, K.-I.; Sakamoto, S.; Touati, M. A.; Kusakawa, Y.; Tadano, K.-I. *Molecules* **2012**, *17*, 13330−13344.

65 Shinada, T.; Oe, K.; Ohfune, Y. *Tetrahedron Lett*. **2012**, *53*, 3250−3253.

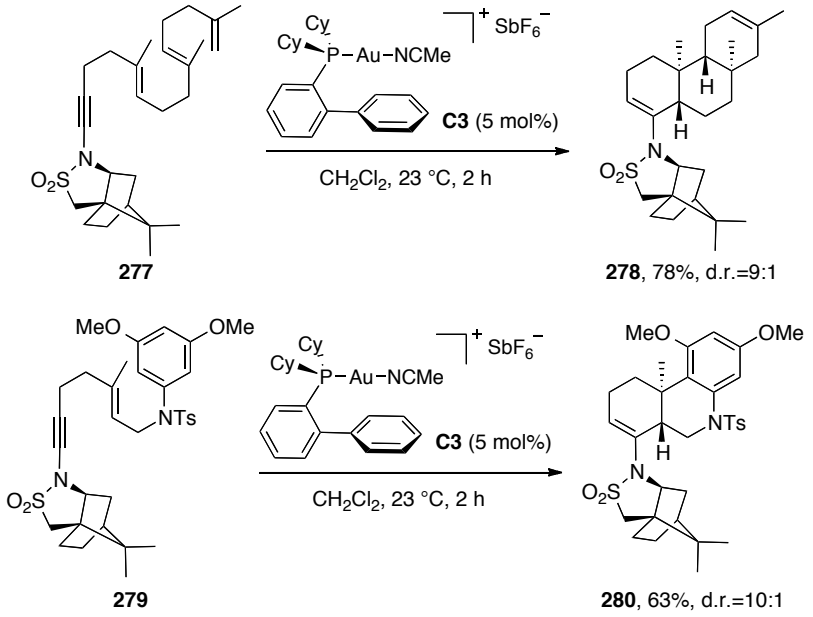
to give spirocyclized product **275** with a 10:1 diastereomeric ratio. We observed that the crude product was partially hydrolyzed after standing in $CDCl_3$ in the presence of gold catalyst. We then carried out the gold(I)-catalyzed cyclization reaction in wet CH_2Cl_2 and found that **275**, formed after 2 h from **274**, could be fully hydrolyzed to **276** after another 16 h (Scheme 58). This demonstrates that the camphorsultam is a chiral auxiliary that can be readily installed and removed.



Scheme 58

We then decided to apply the chiral camphorsultam auxiliary to other substrates. These substrates can be synthesized from the corresponding bromoalkynes in good yields under the same conditions as **274**. Then substrates **277** and **279** underwent gold(I)-catalyzed cyclization to form polycycles **278** and **280** in good yields and good diastereoselectivities

(Scheme 59). The major diastereomer of **280** can be isolated and the absolute configuration was determined by X-ray diffraction (Figure 6).



Scheme 59

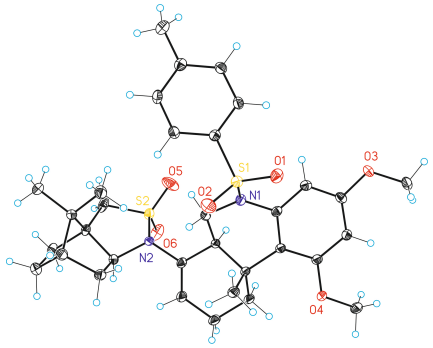
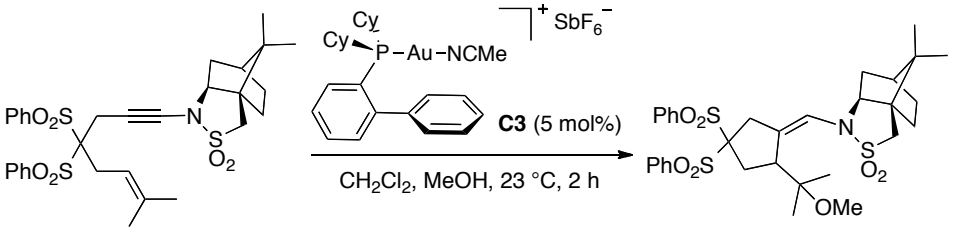


Figure 6. ORTEP plot (50% thermal ellipsoids) of the crystal structure of 280

The camphorsultam auxiliary can also be used in other gold(I)-catalyzed transformations. For example, in the cycloisomerization of 1,6-enyne **281** with methanol as the external nucleophile, the cyclized product could be obtained in 85% yield and 5:1 diastereomeric ratio (Scheme 60). This shows that the chiral camphorsultam auxiliary has large potential in improving other asymmetric gold(I)-catalyzed reactions.



281 **282**, 85%, d.r.=5:1

Scheme 60

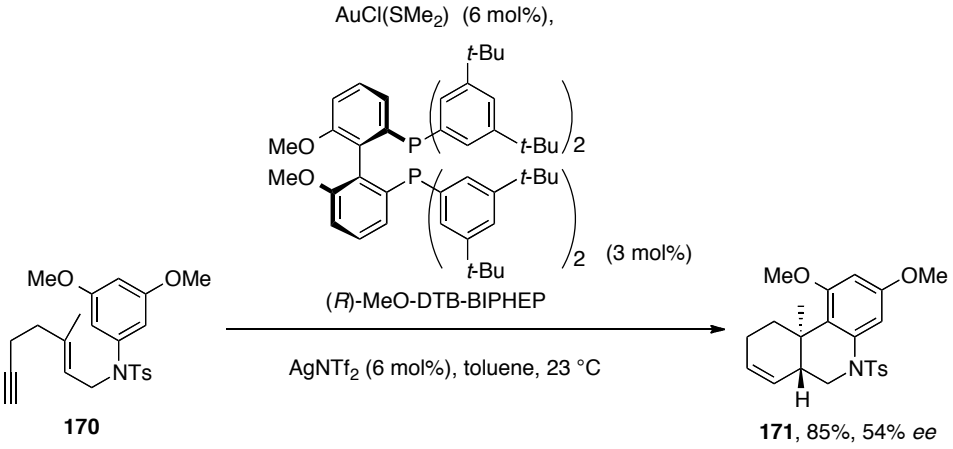
Conclusions

We have explored the gold(I)-catalyzed enantioselective polycyclization. The best result was obtained by employing (*R*)-MeO-DTB-BIPHEP as the chiral ligand, although the enantioselectivities obtained were only low to moderate.

We then turned our attention to the use of chiral camphorsultam auxiliary and found out that it promotes asymmetric gold(I)-catalyzed reactions. The diastereomeric ratios given were satisfactory and the auxiliary could be readily installed and removed. The use of this chiral auxiliary could be a general and practical solution to other asymmetric gold(I)-catalyzed reactions.

Experimental part

1. Representative Procedures for Enantioselective Cyclizations



170

171, 85%, 54% *ee*

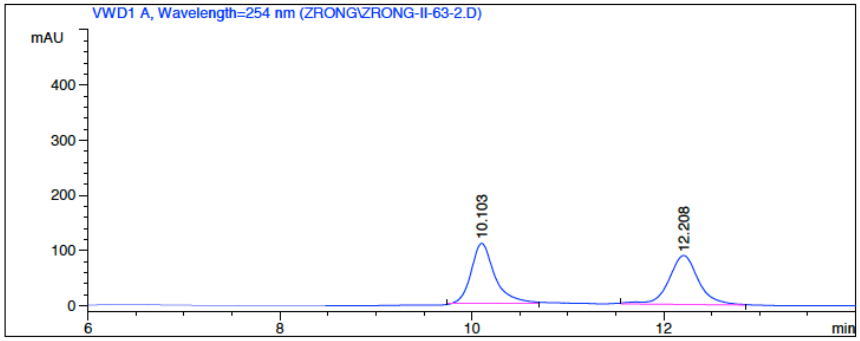
Chloro(dimethylsulfide)gold(I) (1.8 mg, 6 μmol) was added to a solution of (*R*)-MeO- DTBM-BIPHEP (3.0 mg, 3 μmol) in toluene (0.5 mL) and the mixture was stirred at 23 °C for 30 minutes before silver bis(trifluoromethanesulfonyl)imide (2.3 mg, 6 μmol) was added. The mixture was stirred at this temperature for another 30 minutes and a solution of **170** (41 mg, 0.1 mmol) in toluene (0.5 mL) was added. The mixture was stirred at 23 °C for 1 h before it was filtered through a pad of Celite and purified by preparative TLC. The purified product was analyzed on HPLC.

HPLC analysis of racemic **171**.

```
Data File C:\HPCHEM\1\DATA\ZRONG\ZRONG-II-63-2.D
Sample Name: ZRONG-II-63-2

    ======================================================================
    Acq. Operator   : ZHOUTING
    Acq. Instrument : HPLC1100                        Location : Vial 71
    Injection Date  : 3/5/2015 3:33:19 PM
                                                   Inj Volume : 5 µl
    Acq. Method     : C:\HPCHEM\1\DATA\KATYA\MASHA.M
    Last changed    : 3/5/2015 3:28:03 PM by ZHOUTING
                      (modified after loading)
    Analysis Method : C:\HPCHEM\1\DATA\ZRONG\ZRONG-II-63-2.D\DA.M (MASHA.M)
    Last changed    : 1/26/2017 4:54:10 PM by MASHA
    Method Info     : STANDARD FLAVANONE IB

    Sample Info     : chiralpack IA
                      95:5 hex:ipa
                      1.0 ml/min
```

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    ======================================================================
                              Area Percent Report
    ======================================================================

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    Calib. Data Modified  :      10/28/2004 1:11:56 PM
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime  Type   Width     Area      Area     Name
      #   [min]          [min]  mAU   *s       %
    ----|-------|------|-------|----------|--------|--------------------
       1  10.103 MM      0.2917 1922.37549  50.1159 ?
       2  12.208 MM      0.3594 1913.48779  49.8841 ?

    Totals :                  3835.86328
```

HPLC analysis of enantioenriched **171**.

```
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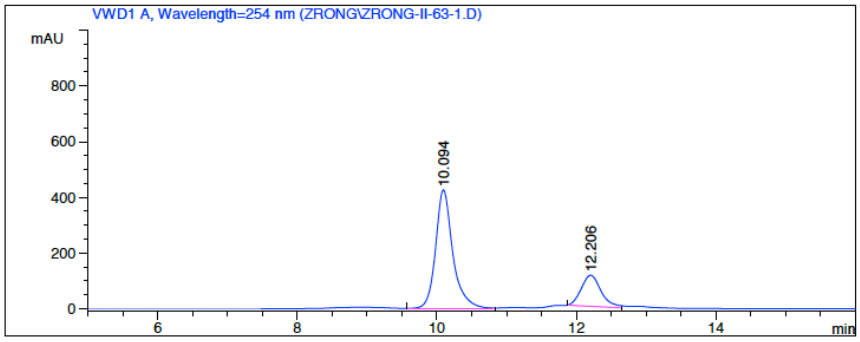
Sample Name: ZRONG-II-63-1

    ======================================================================
    Acq. Operator    : ZHOUTING
    Acq. Instrument : HPLC1100                      Location : Vial 81
    Injection Date   : 3/5/2015 3:54:37 PM
                                                   Inj Volume : 5 µl
    Acq. Method      : C:\HPCHEM\1\DATA\KATYA\MASHA.M
    Last changed     : 3/5/2015 3:51:54 PM by ZHOUTING
                       (modified after loading)
    Analysis Method : C:\HPCHEM\1\DATA\ZRONG\ZRONG-II-63-1.D\DA.M (MASHA.M)
    Last changed     : 1/26/2017 4:17:38 PM by MASHA
                       (modified after loading)
    Method Info      : STANDARD FLAVANONE IB

    Sample Info      : chiralpack IA
                       95:5 hex:ipa
                       1.0 ml/min
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

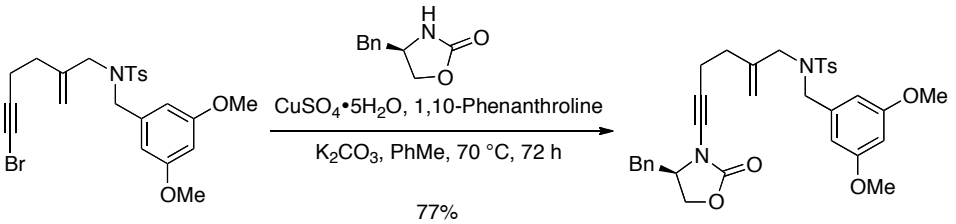
    Sorted By             :      Signal
    Calib. Data Modified  :      10/28/2004 1:11:56 PM
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime  Type   Width     Area      Area     Name
      #   [min]          [min]  mAU   *s       %
    ----|-------|------|-------|----------|--------|--------------------
       1  10.094 VV      0.2607 7396.45166  76.9948 ?
       2  12.206 MM      0.3297 2209.97461  23.0052 ?

    Totals :                  9606.42627
```

2. Representative Procedures for Copper-Catalyzed Cross-Coupling of Bromoalkynes with Auxiliaries



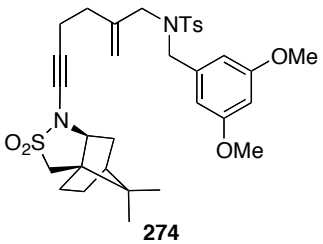
197 **272**

Degassed toluene (2 mL) was added to a 10 ml microwave vial containing **197** (63.3 mg, 0.13 mmol), (*R*)-4-benzyl-2-oxazolidinone (23 mg, 0.13 mmol), $CuSO_4•5H_2O$ (3.2 mg, 0.01 mmol), 1,10-phenanthroline (4.6 mg, 0.02 mmol) and K_2CO_3 (35.5 mg, 0.26 mmol). The vial was purged with Argon and then fitted with a septa and vial seal. The reaction was then heated to 70 °C for 72 hours. The reaction mixture was purified by flash column chromatography (cyclohexane/EtOAc 2:1) to give **272** (59 mg, 77%) as colorless oil. **274** (77%), **277** (70%), **279** (76%) and **281** (88%) can be prepared with the same method.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 - 7.73 (m, 2H), 7.37 - 7.27 (m, 5H), 7.23 - 7.19 (m, 2H), 6.33 (t, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 2.3 Hz, 2H), 5.00 (t, *J* = 1.2 Hz, 1H), 4.93 - 4.91 (m, 1H), 4.33 - 4.26 (m, 3H), 4.21 (tdd, *J* = 8.2, 5.8, 3.9 Hz, 1H), 4.09 (dd, *J* = 8.7, 5.8 Hz, 1H), 3.85 - 3.72 (m, 2H), 3.69 (s, 6H), 3.19 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.90 (dd, *J* = 13.9, 8.3 Hz, 1H), 2.46 - 2.41 (m, 2H), 2.44 (s, 3H), 2.23 - 2.17 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 156.1, 143.3, 142.0, 138.2, 137.4, 134.4, 129.7, 129.4, 129.0, 127.4, 127.2, 115.2, 106.4, 99.9, 72.4, 69.7, 67.2, 58.3, 55.3, 52.2, 51.0, 37.7, 32.1, 21.5, 17.1.

HRMS-ESI calculated for $C_{33}H_{36}N_2NaO_6S$ $[M+Na]^+$: 611.2191; found: 611.2187.

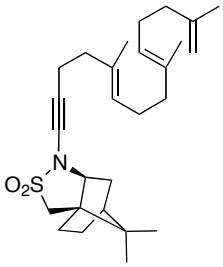


274

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 - 7.73 (m, 2H), 7.35 - 7.31 (m, 2H), 6.34 (t, *J* = 2.3 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 2H), 4.96 (d, *J* = 1.7 Hz, 1H), 4.88 (d, *J* = 1.0 Hz, 1H), 4.29 (s, 2H), 3.74 (m, 2H), 3.71 (s, 6H), 3.51 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.22 (s, 2H), 2.45 (s, 3H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.20 - 2.09 (m, 3H), 1.98 - 1.83 (m, 3H), 1.73 (dd, *J* = 13.3, 8.1 Hz, 1H), 1.46 - 1.37 (m, 1H), 1.35 - 1.29 (m, 1H), 1.10 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 143.3, 141.6, 138.3, 137.5, 129.7, 127.2, 115.3, 106.4, 100.0, 71.5, 68.3, 67.1, 55.3, 51.9, 50.8, 50.7, 49.5, 47.9, 44.4, 34.4, 32.2, 31.6, 27.0, 21.5, 20.2, 19.9, 17.1.

HRMS-ESI calculated for $C_{33}H_{42}N_2NaO_6S_2$ $[M+Na]^+$: 649.2380; found: 649.2374.

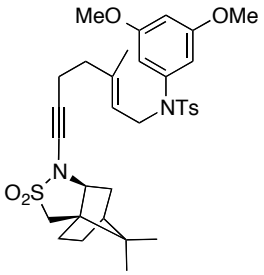


277

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (dtdt, *J* = 13.8, 5.6, 2.7, 1.3 Hz, 2H), 4.75 - 4.69 (m, 2H), 3.52 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.23 (s, 2H), 2.42 - 2.37 (m, 2H), 2.23 - 2.11 (m, 5H), 2.11 - 1.99 (m, 6H), 1.97 - 1.85 (m, 3H), 1.77 - 1.70 (m, 1H), 1.75 (s, 3H), 1.64 - 1.61 (m, 6H), 1.47 - 1.41 (m, 1H), 1.35 - 1.30 (m, 1H), 1.12 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 135.1, 133.4, 125.5, 124.1, 109.8, 72.3, 67.6, 67.1, 50.8, 49.5, 47.9, 44.4, 39.6, 39.0, 37.8, 34.4, 31.6, 27.1, 26.6, 26.2, 22.5, 20.2, 19.9, 18.0, 16.0, 15.8.

HRMS-ESI calculated for $C_{27}H_{41}NNaO_2S$ $[M+Na]^+$: 466.2754; found: 466.2747.

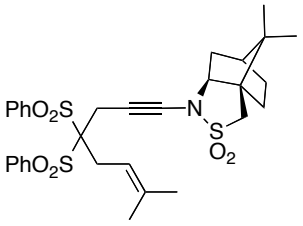


279

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 - 7.54 (m, 2H), 7.28 - 7.26 (m, 2H), 6.37 (t, *J* = 2.3 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 2H), 5.15 (ddd, *J* = 8.2, 4.2, 2.8 Hz, 1H), 4.15 - 4.11 (m, 2H), 3.71 (s, 6H), 3.49 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.21 (s, 2H), 2.43 (s, 3H), 2.26 (dd, *J* = 8.1, 7.0 Hz, 2H), 2.18 - 2.08 (m, 3H), 1.98 - 1.81 (m, 3H), 1.77 - 1.69 (m, 1H), 1.55 - 1.51 (m, 3H), 1.45 - 1.38 (m, 1H), 1.35 - 1.29 (m, 1H), 1.08 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 143.4, 141.2, 138.7, 135.7, 129.4, 127.8, 120.0, 106.9, 100.1, 71.7, 68.1, 67.1, 55.4, 50.9, 49.5, 48.6, 47.9, 44.4, 38.7, 34.4, 31.6, 27.0, 21.5, 20.2, 19.9, 17.8, 16.1.

HRMS-ESI calculated for $C_{33}H_{42}N_2NaO_6S_2$ $[M+Na]^+$: 649.2380; found: 649.2372.



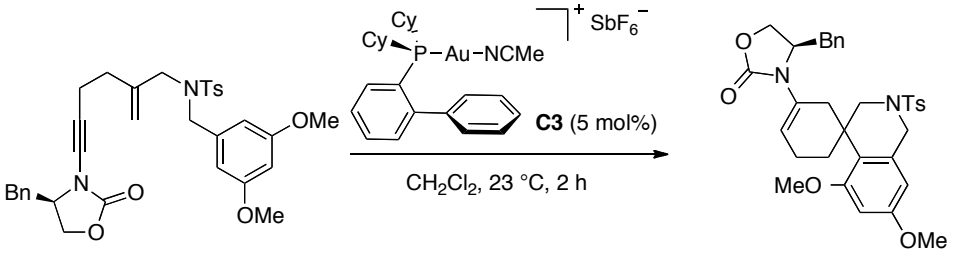
281

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 - 8.10 (m, 4H), 7.74 - 7.67 (m, 2H), 7.62 - 7.56 (m, 4H), 5.37 (tt, *J* = 6.6, 1.4 Hz, 1H), 3.55 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.28 (s, 2H), 3.24 (s, 2H), 3.12 - 2.95 (m, 2H), 2.27 - 2.17 (m, 1H), 1.97 - 1.85 (m, 3H), 1.79 - 1.70 (m, 4H), 1.63 - 1.59 (m, 3H), 1.46 - 1.39 (m, 1H), 1.34 - 1.28 (m, 1H), 1.08 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 136.7, 136.7, 134.6, 131.5, 128.6, 128.5, 115.0, 89.3, 73.0, 67.0, 65.2, 51.2, 49.8, 47.9, 44.4, 34.5, 31.6, 28.1, 27.0, 26.1, 21.4, 20.2, 19.9, 18.3.

HRMS-ESI calculated for $C_{31}H_{37}NNaO_6S_3$ $[M+Na]^+$: 638.1680; found: 638.1674.

3. Representative Procedures for Auxiliary-Promoted Gold(I)-Catalyzed Asymmetric Cyclization



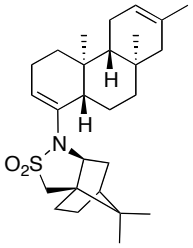
272 **273**, 73%, d.r.=5:1

C3 (2.2 mg, 2.7 μmol) was added to a solution of **272** (32 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) and the mixture was stirred at 23 °C for 2 h. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 2:1) to give **273** (23.4 mg, 73%, d.r.=5:1) as colorless oil. **278** (78%, d.r.=9:1), **280** (63%, d.r.=10:1) and **282** (85%, d.r.=5:1) can be prepared with the same method.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 - 7.71 (m, 2H), 7.36 - 7.30 (m, 5H), 7.22 - 7.19 (m, 2H), 6.38 (d, *J* = 2.5 Hz, 1H), 6.20 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.89 (dt, *J* = 4.9, 2.3 Hz, 1H), 4.31 (dddd, *J* = 10.1, 8.5, 5.3, 3.5 Hz, 1H), 4.22 - 4.16 (m, 2H), 4.13 - 4.05 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.58 (dd, *J* = 18.0, 3.2 Hz, 1H), 3.33 (dd, *J* = 13.8, 3.4 Hz, 1H), 3.17 - 3.07 (m, 2H), 2.76 - 2.66 (m, 2H), 2.43 (m, 1H), 2.43 (s, 3H), 2.32 - 2.24 (m, 1H), 2.10 - 2.04 (m, 1H), 1.56 (dd, *J* = 13.5, 5.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.9, 155.6, 143.7, 135.9, 134.5, 132.9, 131.7, 129.8, 129.1, 128.9, 127.8, 127.8, 127.1, 121.6, 117.7, 102.3, 98.6, 66.4, 57.0, 55.3, 52.7, 50.0, 38.3, 37.7, 33.6, 27.1, 21.5, 21.3.

HRMS-ESI calculated for $C_{33}H_{36}N_2NaO_6S$ $[M+Na]^+$: 611.2191; found: 611.2185.

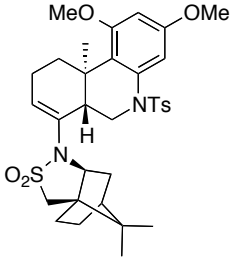


278, d.r.=9:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (q, *J* = 3.1 Hz, 1H), 5.37 - 5.34 (m, 1H), 3.52 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.17 (d, *J* = 10.9 Hz, 2H), 2.18 (dq, *J* = 8.8, 3.2, 2.7 Hz, 4H), 2.14 - 2.04 (m, 3H), 1.89 (dq, *J* = 11.5, 4.5 Hz, 5H), 1.77 - 1.72 (m, 2H), 1.69 - 1.66 (m, 1H), 1.64 - 1.62 (m, 3H), 1.55 - 1.50 (m, 2H), 1.32 (d, *J* = 4.0 Hz, 1H), 1.24 - 1.19 (m, 3H), 1.18 (s, 3H), 0.95 (s, 3H), 0.95 (s, 3H), 0.80 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.0, 132.4, 122.1, 119.9, 65.9, 51.5, 49.7, 49.6, 49.1, 48.8, 47.5, 44.3, 41.9, 36.4, 35.3, 34.2, 33.0, 32.5, 27.0, 23.7, 23.3, 22.5, 21.0, 20.7, 20.6, 20.3, 12.3.

HRMS-ESI calculated for $C_{27}H_{41}NNaO_2S$ $[M+Na]^+$: 466.2754; found: 466.2749.

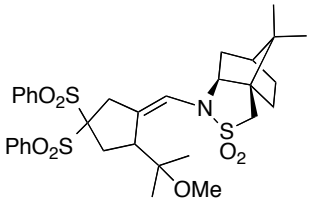


280, d.r.=10:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.26 - 7.24 (m, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 5.72 (q, *J* = 3.4 Hz, 1H), 4.82 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.73 (d, *J* = 0.8 Hz, 6H), 3.55 (dd, *J* = 7.8, 5.1 Hz, 1H), 3.29 - 3.21 (m, 3H), 3.08 (ddd, *J* = 13.4, 5.4, 2.5 Hz, 1H), 2.73 (dq, *J* = 13.2, 3.5 Hz, 1H), 2.39 (s, 3H), 2.27 (tq, *J* = 5.4, 3.2, 2.7 Hz, 2H), 1.98 - 1.87 (m, 3H), 1.82 - 1.76 (m, 1H), 1.71 (dd, *J* = 13.0, 7.8 Hz, 1H), 1.57 - 1.52 (m, 1H), 1.43 - 1.38 (m, 1H), 1.35 - 1.30 (m, 1H), 1.28 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.2, 143.4, 137.8, 137.1, 130.3, 129.6, 127.3, 124.1, 118.4, 98.9, 95.4, 65.6, 55.4, 55.2, 49.6, 49.0, 47.6, 46.2, 44.3, 43.4, 36.3, 35.5, 32.5, 31.0, 27.0, 23.0, 21.5, 20.4, 20.2, 17.1.

HRMS-ESI calculated for $C_{33}H_{42}N_2NaO_6S_2$ $[M+Na]^+$: 649.2380; found: 649.2375.

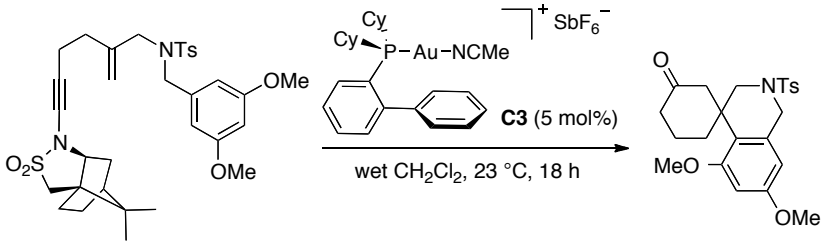


282, d.r.=5:1

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 - 8.05 (m, 4H), 7.74 - 7.68 (m, 2H), 7.60 (ddt, *J* = 8.1, 7.2, 1.9 Hz, 4H), 5.22 (ddt, *J* = 6.1, 4.6, 2.3 Hz, 1H), 4.68 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.65 (s, 3H), 3.38 (dd, *J* = 7.7, 4.1 Hz, 1H), 3.34 - 3.26 (m, 3H), 2.97 - 2.87 (m, 3H), 1.93 - 1.89 (m, 4H), 1.78 (dd, *J* = 12.8, 7.7 Hz, 1H), 1.68 (q, *J* = 1.4 Hz, 3H), 1.55 (d, *J* = 1.5 Hz, 3H), 1.47 (t, *J* = 9.3 Hz, 1H), 1.35 (d, *J* = 7.1 Hz, 1H), 1.18 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 137.2, 137.1, 136.2, 134.4, 131.4, 131.4, 128.5, 128.5, 115.7, 95.5, 90.2, 64.7, 58.8, 51.2, 49.5, 47.7, 44.5, 36.1, 32.4, 29.0, 26.8, 26.2, 25.9, 20.4, 20.0, 18.1.

HRMS-ESI calculated for $C_{31}H_{37}NNaO_6S_3$ $[M+Na]^+$: 638.1680; found: 638.1675.



274 **276**, 55%

C3 (1.6 mg, 2.0 μmol) was added to a solution of **274** (25.4 mg, 0.04 mmol) in wet CH_2Cl_2 (1 mL) and the mixture was stirred at 23 °C for 18 h. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane/EtOAc 2:1) to give **276** (9.6 mg, 55%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 - 7.72 (m, 2H), 7.39 - 7.36 (m, 2H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 4.57 - 4.50 (m, 1H), 3.77 (s, 3H), 3.75 - 3.68 (m, 2H), 3.73 (s, 3H), 3.24 (d, *J* = 15.5 Hz, 1H), 2.46 (s, 3H), 2.42 (dd, *J* = 7.2, 5.8 Hz, 2H), 2.36 - 2.31 (m, 1H), 2.23 (ddd, *J* = 14.8, 9.5, 5.9 Hz, 1H), 2.11 - 2.02 (m, 1H), 2.02 - 1.92 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8, 159.1, 158.7, 143.9, 133.6, 132.8, 129.8, 127.8, 121.5, 102.2, 98.2, 55.3, 54.4, 53.8, 49.1, 48.5, 40.6, 40.3, 31.8, 21.5, 20.8.

HRMS-ESI calculated for $C_{23}H_{27}NNaO_5S$ $[M+Na]^+$: 452.1506; found: 452.1501.

Crystal data

Compound 280

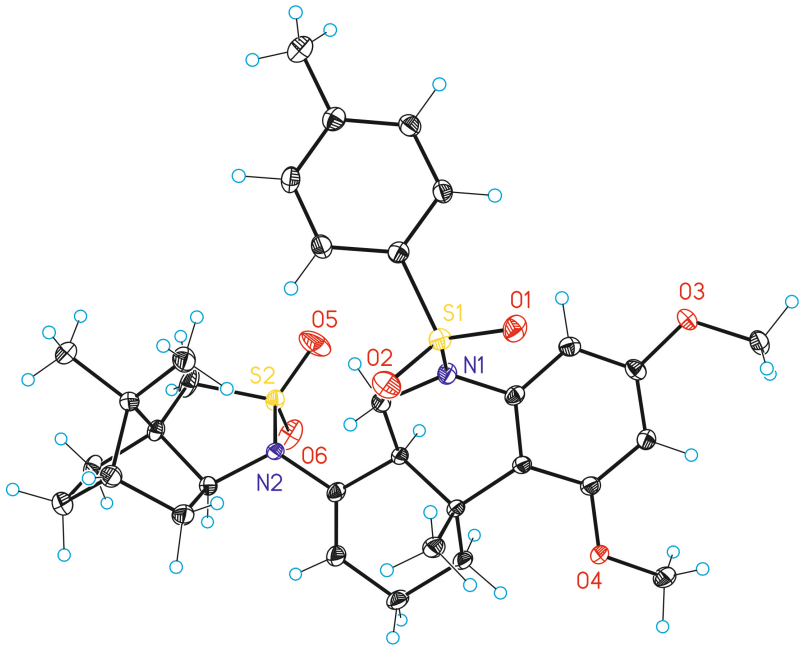


Table 1. Crystal data and structure refinement for mo_zrii155_0m.

Identification code	mo_zrii155_0m	
Empirical formula	C33 H42 N2 O6 S2	
Formula weight	626.80	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.4833(3)Å	a= 90°.
	b = 13.5940(4)Å	b = 96.5887(9)°.
	c = 10.7527(3)Å	g = 90°.
Volume	1522.25(8) $Å^3$	
Z	2	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	0.224 mm^{-1}	
F(000)	668	
Crystal size	0.20 x 0.20 x 0.01 mm^3	
Theta range for data collection	1.907 to 31.021°.	
Index ranges	-15<=h<=14,-14<=k<=19,-15<=l<=14	
Reflections collected	16384	
Independent reflections	7064[R(int) = 0.0243]	
Completeness to theta =31.021°	97.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.998 and 0.955	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7064/ 1/ 394	
Goodness-of-fit on F^2	1.038	

Final R indices [I>2sigma(I)]	R1 = 0.0333, wR2 = 0.0780
R indices (all data)	R1 = 0.0411, wR2 = 0.0820
Flack parameter	x =-0.03(2)
Largest diff. peak and hole	0.283 and -0.322 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for mo_zrii155_0m.

Bond lengths----	
C1-C2	1.390(3)
C1-C6	1.406(3)
C1-N1	1.436(3)
C2-C3	1.388(3)
C3-O3	1.374(3)
C3-C4	1.391(3)
C4-C5	1.394(3)
C5-O4	1.361(3)
C5-C6	1.409(3)
C6-C7	1.531(3)
C7-C16	1.540(3)
C7-C8	1.549(3)
C7-C12	1.556(3)
C8-C9	1.529(3)
C9-C10	1.499(3)
C10-C11	1.325(3)
C11-N2	1.451(3)
C11-C12	1.522(3)
C12-C13	1.527(3)
C13-N1	1.482(3)
C14-O3	1.429(3)
C15-O4	1.425(3)
C17-N2	1.479(3)
C17-C18	1.545(3)
C17-C22	1.546(3)
C18-C19	1.546(3)
C19-C20	1.542(4)
C19-C23	1.547(3)
C20-C21	1.549(4)

C21-C22	1.540(3)
C22-C26	1.515(3)
C22-C23	1.557(3)
C23-C25	1.536(3)
C23-C24	1.538(3)
C26-S2	1.787(2)
C27-C32	1.389(3)
C27-C28	1.391(3)
C27-S1	1.759(2)
C28-C29	1.386(3)
C29-C30	1.392(3)
C30-C31	1.392(3)
C30-C33	1.505(3)
C31-C32	1.385(3)
N1-S1	1.6540(19)
N2-S2	1.6763(19)
O1-S1	1.4316(17)
O2-S1	1.4368(16)
O5-S2	1.4337(19)
O6-S2	1.4356(18)

Angles----------

C2-C1-C6	122.91(19)
C2-C1-N1	118.70(19)
C6-C1-N1	118.37(19)
C3-C2-C1	118.8(2)
O3-C3-C2	116.2(2)
O3-C3-C4	123.4(2)
C2-C3-C4	120.4(2)
C3-C4-C5	119.48(19)
O4-C5-C4	121.62(19)
O4-C5-C6	116.28(19)

C4-C5-C6	122.0(2)
C1-C6-C5	115.70(19)
C1-C6-C7	117.87(18)
C5-C6-C7	126.42(18)
C6-C7-C16	110.36(18)
C6-C7-C8	113.21(17)
C16-C7-C8	110.26(18)
C6-C7-C12	105.54(16)
C16-C7-C12	111.15(17)
C8-C7-C12	106.17(18)
C9-C8-C7	111.87(18)
C10-C9-C8	112.79(19)
C11-C10-C9	123.0(2)
C10-C11-N2	121.3(2)
C10-C11-C12	123.2(2)
N2-C11-C12	115.55(18)
C11-C12-C13	110.51(17)
C11-C12-C7	111.83(17)
C13-C12-C7	111.05(18)
N1-C13-C12	109.96(17)
N2-C17-C18	114.67(18)
N2-C17-C22	105.99(17)
C18-C17-C22	103.80(16)
C17-C18-C19	102.06(18)
C20-C19-C18	107.8(2)
C20-C19-C23	102.28(19)
C18-C19-C23	102.81(17)
C19-C20-C21	103.24(18)
C22-C21-C20	102.75(19)
C26-C22-C21	118.2(2)
C26-C22-C17	108.74(17)
C21-C22-C17	105.00(18)

C26-C22-C23	117.8(2)
C21-C22-C23	101.36(17)
C17-C22-C23	104.18(17)
C25-C23-C24	106.61(19)
C25-C23-C19	114.5(2)
C24-C23-C19	115.38(18)
C25-C23-C22	116.15(18)
C24-C23-C22	111.50(18)
C19-C23-C22	92.57(17)
C22-C26-S2	105.99(15)
C32-C27-C28	120.7(2)
C32-C27-S1	119.72(16)
C28-C27-S1	119.57(17)
C29-C28-C27	119.2(2)
C28-C29-C30	121.0(2)
C29-C30-C31	118.7(2)
C29-C30-C33	120.5(2)
C31-C30-C33	120.7(2)
C32-C31-C30	121.1(2)
C31-C32-C27	119.2(2)
C1-N1-C13	120.56(17)
C1-N1-S1	120.19(15)
C13-N1-S1	115.55(13)
C11-N2-C17	118.82(17)
C11-N2-S2	113.69(14)
C17-N2-S2	107.15(14)
C3-O3-C14	116.35(18)
C5-O4-C15	119.15(18)
O1-S1-O2	119.04(10)
O1-S1-N1	108.33(9)
O2-S1-N1	108.30(10)
O1-S1-C27	109.12(10)

O2-S1-C27	106.91(10)
N1-S1-C27	104.16(10)
O5-S2-O6	116.25(12)
O5-S2-N2	109.03(10)
O6-S2-N2	111.15(10)
O5-S2-C26	112.83(13)
O6-S2-C26	109.44(12)
N2-S2-C26	96.38(10)

Table 3. Torsion angles [°] for mo_zrii155_0m.

C6-C1-C2-C3	-6.1(3)
N1-C1-C2-C3	172.1(2)
C1-C2-C3-O3	179.48(19)
C1-C2-C3-C4	-0.7(3)
O3-C3-C4-C5	-177.0(2)
C2-C3-C4-C5	3.2(3)
C3-C4-C5-O4	-175.5(2)
C3-C4-C5-C6	0.9(3)
C2-C1-C6-C5	9.8(3)
N1-C1-C6-C5	-168.47(19)
C2-C1-C6-C7	-169.0(2)
N1-C1-C6-C7	12.7(3)
O4-C5-C6-C1	169.45(19)
C4-C5-C6-C1	-7.1(3)
O4-C5-C6-C7	-11.8(3)
C4-C5-C6-C7	171.6(2)
C1-C6-C7-C16	-85.3(2)
C5-C6-C7-C16	96.0(2)
C1-C6-C7-C8	150.6(2)
C5-C6-C7-C8	-28.1(3)
C1-C6-C7-C12	34.9(2)
C5-C6-C7-C12	-143.8(2)
C6-C7-C8-C9	-178.60(19)
C16-C7-C8-C9	57.2(3)
C12-C7-C8-C9	-63.3(2)
C7-C8-C9-C10	43.5(3)
C8-C9-C10-C11	-10.6(3)
C9-C10-C11-N2	-179.9(2)
C9-C10-C11-C12	-0.4(4)
C10-C11-C12-C13	-145.5(2)

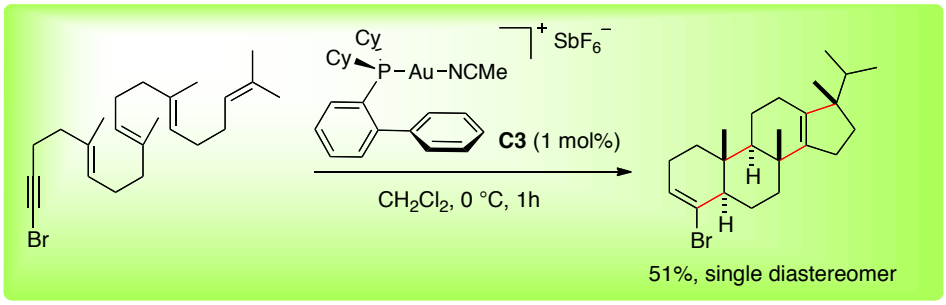
N2-C11-C12-C13	34.0(2)
C10-C11-C12-C7	-21.2(3)
N2-C11-C12-C7	158.28(17)
C6-C7-C12-C11	171.03(17)
C16-C7-C12-C11	-69.3(2)
C8-C7-C12-C11	50.6(2)
C6-C7-C12-C13	-65.0(2)
C16-C7-C12-C13	54.6(2)
C8-C7-C12-C13	174.56(17)
C11-C12-C13-N1	170.58(17)
C7-C12-C13-N1	45.9(2)
N2-C17-C18-C19	121.8(2)
C22-C17-C18-C19	6.7(2)
C17-C18-C19-C20	66.9(2)
C17-C18-C19-C23	-40.7(2)
C18-C19-C20-C21	-73.8(2)
C23-C19-C20-C21	34.2(2)
C19-C20-C21-C22	2.6(2)
C20-C21-C22-C26	-168.7(2)
C20-C21-C22-C17	69.9(2)
C20-C21-C22-C23	-38.3(2)
N2-C17-C22-C26	34.4(2)
C18-C17-C22-C26	155.6(2)
N2-C17-C22-C21	161.80(17)
C18-C17-C22-C21	-77.0(2)
N2-C17-C22-C23	-92.05(18)
C18-C17-C22-C23	29.1(2)
C20-C19-C23-C25	-176.01(18)
C18-C19-C23-C25	-64.3(2)
C20-C19-C23-C24	59.7(2)
C18-C19-C23-C24	171.4(2)
C20-C19-C23-C22	-55.65(19)

C18-C19-C23-C22	56.1(2)
C26-C22-C23-C25	-53.1(3)
C21-C22-C23-C25	176.3(2)
C17-C22-C23-C25	67.5(2)
C26-C22-C23-C24	69.3(2)
C21-C22-C23-C24	-61.3(2)
C17-C22-C23-C24	-170.15(17)
C26-C22-C23-C19	-172.08(19)
C21-C22-C23-C19	57.3(2)
C17-C22-C23-C19	-51.54(19)
C21-C22-C26-S2	-132.10(19)
C17-C22-C26-S2	-12.6(2)
C23-C22-C26-S2	105.5(2)
C32-C27-C28-C29	1.8(3)
S1-C27-C28-C29	-177.06(19)
C27-C28-C29-C30	-1.3(4)
C28-C29-C30-C31	-0.3(4)
C28-C29-C30-C33	179.1(2)
C29-C30-C31-C32	1.6(3)
C33-C30-C31-C32	-177.9(2)
C30-C31-C32-C27	-1.2(3)
C28-C27-C32-C31	-0.6(3)
S1-C27-C32-C31	178.28(17)
C2-C1-N1-C13	146.1(2)
C6-C1-N1-C13	-35.6(3)
C2-C1-N1-S1	-56.6(3)
C6-C1-N1-S1	121.80(19)
C12-C13-N1-C1	4.2(3)
C12-C13-N1-S1	-154.16(15)
C10-C11-N2-C17	25.3(3)
C12-C11-N2-C17	-154.19(18)
C10-C11-N2-S2	-102.2(2)

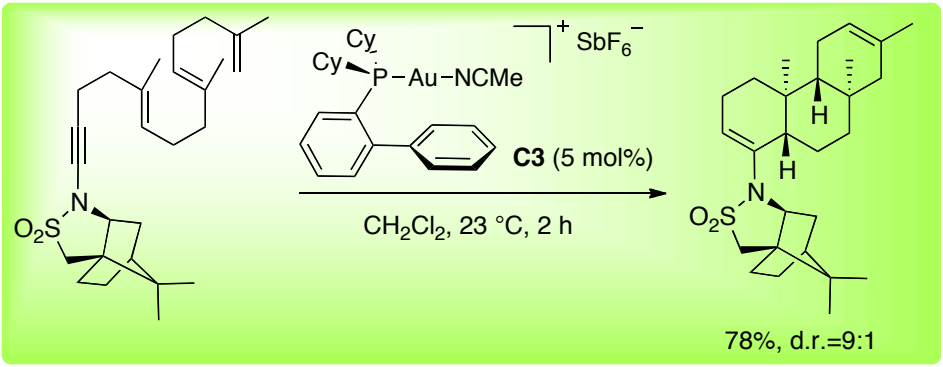
C12-C11-N2-S2	78.3(2)
C18-C17-N2-C11	73.8(2)
C22-C17-N2-C11	-172.35(18)
C18-C17-N2-S2	-155.70(15)
C22-C17-N2-S2	-41.83(18)
C2-C3-O3-C14	151.1(2)
C4-C3-O3-C14	-28.6(3)
C4-C5-O4-C15	-9.1(3)
C6-C5-O4-C15	174.3(2)
C1-N1-S1-O1	7.8(2)
C13-N1-S1-O1	166.27(16)
C1-N1-S1-O2	-122.59(17)
C13-N1-S1-O2	35.87(19)
C1-N1-S1-C27	123.87(17)
C13-N1-S1-C27	-77.67(17)
C32-C27-S1-O1	25.8(2)
C28-C27-S1-O1	-155.29(18)
C32-C27-S1-O2	155.81(17)
C28-C27-S1-O2	-25.3(2)
C32-C27-S1-N1	-89.67(19)
C28-C27-S1-N1	89.20(19)
C11-N2-S2-O5	-78.73(18)
C17-N2-S2-O5	147.93(15)
C11-N2-S2-O6	50.70(18)
C17-N2-S2-O6	-82.64(15)
C11-N2-S2-C26	164.42(17)
C17-N2-S2-C26	31.09(16)
C22-C26-S2-O5	-124.03(18)
C22-C26-S2-O6	104.85(18)
C22-C26-S2-N2	-10.26(19)

General Conclusions

1. The scope of gold(I)-catalyzed polycyclization of 1,5-enynes has been studied. We found that polyenynes bearing internal nucleophiles such as electron-rich aromatic rings, hydroxyl groups, and alkenes undergo polycyclization reactions to give fused- and spiropolycyclic compounds by using a cationic gold(I) catalyst. 1-Bromo-1,5-enynes were also found to be appropriate substrates for gold(I)-catalyzed polycyclizations. These polycyclization reactions allow the formation of up to four carbon-carbon bonds and four fused-rings in a single transformation.



2. We explored the development of asymmetric gold(I)-catalyzed polycyclization was made. While the enantioselective polycyclization by generating chiral cationic gold(I) catalyst *in situ* was not successful, a chiral camphorsultam auxiliary was found to be a good alternative. This camphorsultam auxiliary can be readily installed and removed and it gives the polycyclized products in good diastereoselectivities.



Appendix

Gold Catalysis Hot Paper

DOI: 10.1002/anie.201404029

Formal (4+1) Cycloaddition of Methylenecyclopropanes with 7-Aryl-1,3,5-cycloheptatrienes by Triple Gold(I) Catalysis**

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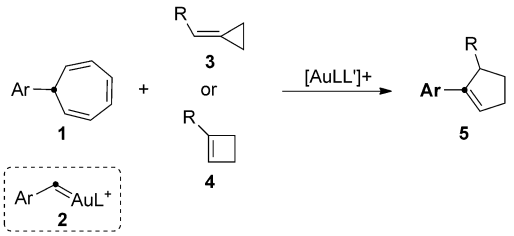
Abstract: *7-Aryl-1,3,5-cycloheptatrienes react intermolecularly with methylenecyclopropanes in a triple gold(I)-catalyzed reaction to form cyclopentenes. The same formal (4+1) cycloaddition occurs with cyclobutenes. Other precursors of gold(I) carbenes can also be used as the C_1 component of the cycloaddition.*

Carbenes have been widely used as one-carbon synthon in organic synthesis, particularly in the context of cyclopropanation reactions.[1] However, only a few (4+1) cycloadditions[2] have been reported mainly with Fischer alkoxy(alkenyl)carbene complexes[3] and dialkoxycarbenes.[2,4] To the best of our knowledge, there is no report on the (4+1) cycloaddition of aryl carbenes with 1,3-dienes, probably because of the known propensity of carbenes to give cyclopropanation products with 1,3-dienes.[5] We postulated that due to their high strain and unique electronic properties, cyclobutenes[6] could be used as synthetic equivalents of 1,3-dienes for the development of a formal (4+1) cycloaddition with metal carbenes.

We have recently found that 7-substituted 1,3,5-cycloheptatrienes **1** undergo gold(I)-catalyzed retro-Buchner reaction to form carbenes **2** (Scheme 1).[7] Herein, we report a novel and potentially general formal (4+1) cycloaddition by reaction of **1** with methylenecyclopropanes **3**[8] or cyclobutenes **4** to form cyclopentenes **5**. In this transformation, methylenecyclopropanes **3** undergo an isomerization to form cyclobutenes **4** similar to that catalyzed by platinum or palladium.[9] Therefore, in the reaction between **1** and **3**, gold(I) plays a triple catalytic role, isomerizing **3** into **4** and, in parallel, generating gold(I) carbenes **2** from **1**, which cyclopropanate the cyclobutenes. Finally, gold(I) cleaves the internal C–C bond of the resulting bicyclo[2.1.0]pentanes to form the cyclopentenes. This reaction can be viewed as an insertion of one carbon into a double bond, a process that has only been achieved in rare cases with dihalocarbenes.[10,11]



Scheme 1. New strategy for the formal (4+1) cycloaddition.

Methylenecyclopropanes (MCPs) **3** can be readily prepared in one step by the Wittig olefination of carbonyl compounds with commercially available 3-bromo-triphenylphosphonium bromide. We first examined the reaction of phenylmethylenecyclopropane (**3a**) with 7-naphthyl-cyclohepta-1,3,5-triene (**1a**) in the presence of gold(I) complexes (Table 1). Using cationic [(JohnPhos)Au(MeCN)]SbF_6 (**A**) in 1,2-dichloroethane at 120 °C, disubstituted cyclopentene **5a** was isolated in 76 % yield (Table 1, entry 1). Other phosphine or N-heterocyclic carbene gold(I) complexes **B**–**E** gave lower yields (entries 2–5), whereas complexes **F** and **G** failed to promote this transformation, presumably due to their instability at the temperature required for the retro-Buchner reaction. The reaction also failed with silver(I), copper(II), and platinum(II) catalysts (entries 8–10).

7-Aryl-cyclohepta-1,3,5-trienes containing groups with different electronic and steric effects at the *ortho*, *meta*, or *para* positions reacted with MCPs **3a**–**h** to yield the (4+1) cycloadducts **5b**–**m** (Table 2). The (4+1) cycloaddition proceeds satisfactorily with MCP bearing arenes with fluoro-, chloro-, and bromo-substituents. However, the reaction with *o*-bromophenylmethylenecyclopropane (**3f**) led to cycloadduct **5k** in lower yield. The structure of **5k** was confirmed by X-ray diffraction (Figure 1).[12] To demonstrate the synthetic utility of this method, cyclopentene **5l** was prepared on a 500 mg scale using only 1 mol % gold catalyst **A** in 51 % yield after purification by column chromatography. Alkylmethylenecyclopropanes also reacted to give (4+1) cycloaddition products, although in this case the reactions led to mixtures of regioisomers **5n/n′**–**5p/p′**.

Substrate **3l** reacted intramolecularly using catalyst **E** to form 2,3-dihydro-1*H*-cyclopenta[*l*]phenanthrene (**5q′**) by iso-

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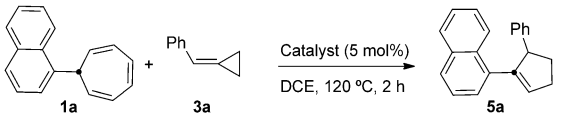
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404029.

Table 1: Gold(I)-catalyzed reaction of 7-(1-naphtyl)-1,3,5-cycloheptatriene (**1a**) with phenylmethylenecyclopropane (**3a**).[a]



Entry	Catalyst	Yield [%][b]
1	**A**	81 (76)[c]
2	**B**	25
3	**C**	28
4	**D**	< 5
5	**E**	47
6	**F**	–[d]
7	**G**	–[d]
8	**H**	–[d]
9	**I**	–[d]
10	**J**	–[d]

[a] Reaction at 120 °C (0.2 M in 1,2-dichloroethane), 2 equiv of **3a**, catalyst (5 mol%), 2 h. [b] Yields determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard. [c] Yield of isolated product. [d] Not detected.

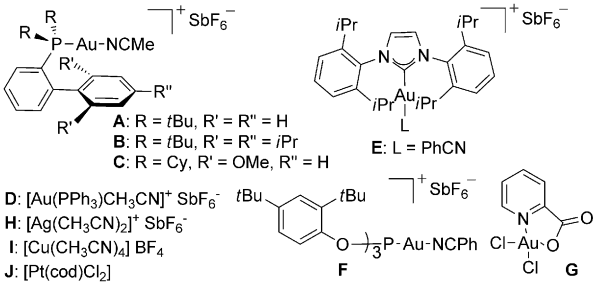
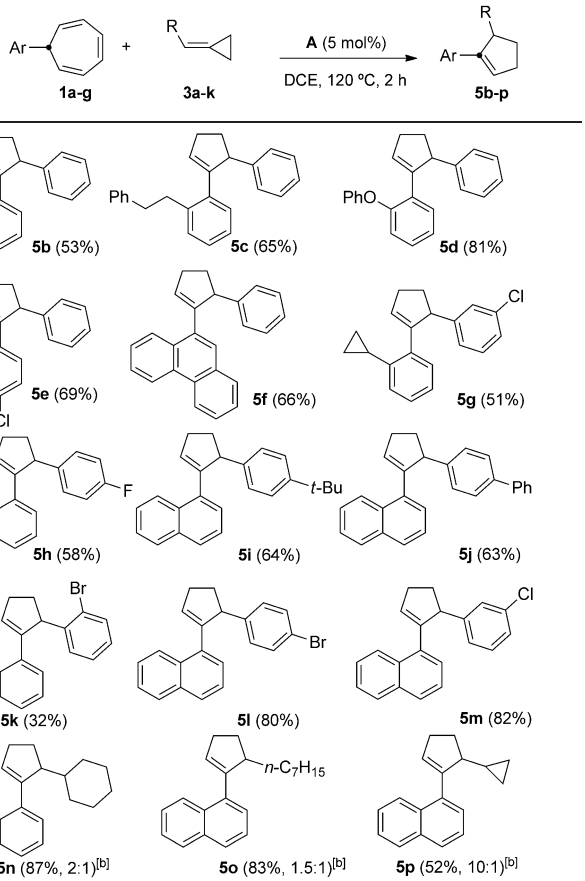


Table 2: Scope of the formal (4+1) cycloaddition between cycloheptatrienes **1** and methylenecyclopropanes **3**.[a]



[a] Reaction at 120 °C, 0.2 M in 1,2-dichloroethane, 2 equiv of **3a–k**, catalyst **A** (5 mol%), 2 h. Yields are for isolated products. [b] Reaction time = 3 h. 3-Alkyl-3-arylcyclopent-1-enes **5′n–p** were also obtained as minor regioisomers.

merization of the initially formed adduct **5q** (Scheme 2). In addition, polyarene fragments can be obtained by photochemical cyclization. Thus, compound **5f** can be transformed into a cyclopenta derivative of benzo[*g*]chrysene (**6**) by a one pot photo-induced isomerization/oxidative Mallory cyclization.[13]

Tetrasubstituted MCP **3m** reacted with **1a** to give only the product of cyclopropanation **7** (Scheme 3 and Figure 1), whose structure was confirmed by X-ray diffraction (Figure 1).[12] Given that **3m** does not undergo ring-expansion, the isolation of spiro derivative **7** strongly suggests that the cyclopropanation of MCP is not the initial step in the formal (4+1) cycloaddition and that cyclobutenes are likely intermediates in this transformation.

To confirm the hypothesis that cyclobutenes are intermediates in the (4+1) reaction of MCP, we performed the reaction of **1a** with cyclobutene **4a**, which was isolated from the reaction mixture of **1a** and **3g**. Under identical conditions, cycloadduct **5l** was isolated in 77% yield. Trisubstituted cyclobutenes[14] also took part in the (4+1) cycloaddition reaction to afford cyclopentenes **5r–z** (Table 3).

Cyclobutenes also react with intermediate gold(I) carbenes generated by 1,2-acyloxy migration of propargylic acetates[15] under mild conditions with catalyst **E** to give two separable isomers **5aa–ac** and **5′aa–ac** in good overall yields (Scheme 4). By performing the reaction at room temperature

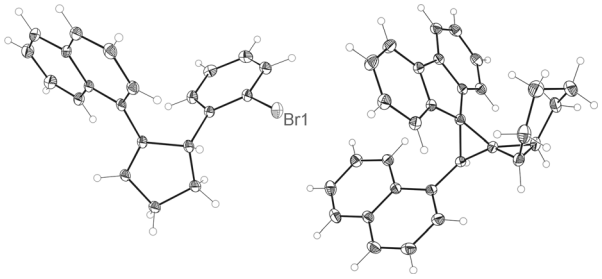
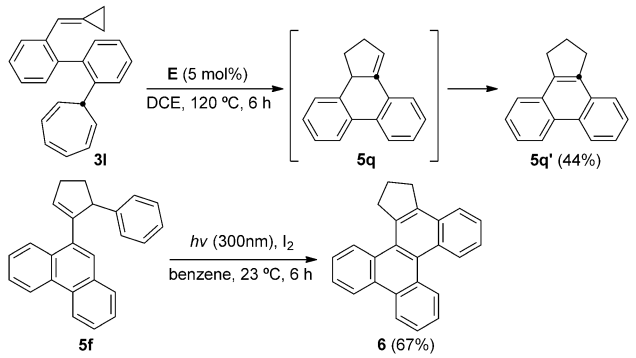
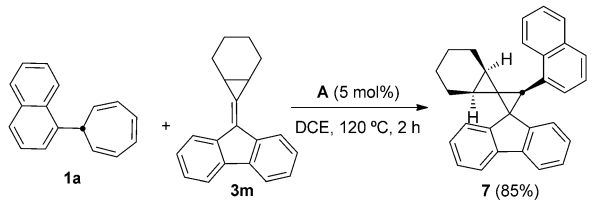


Figure 1. X-ray crystal structures of **5k** and **7**.

at only 60% conversion, bicyclo[2.1.0]pentane **10a**[16] could be isolated and then transformed cleanly into **5aa** at 40 °C in the presence of gold(I) catalyst. The gold(I) carbene generated from phenyl diazomethane[17–20] reacted similarly at room temperature with cyclobutene **4c** to form the desired formal (4+1) product **5ad**, along with **10b**.[21] This bicyclo[2.1.0]pentane was converted quantitatively into cyclopentene **5ad** by warming at 60 °C in the presence of gold complex **A**.

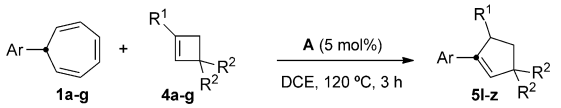


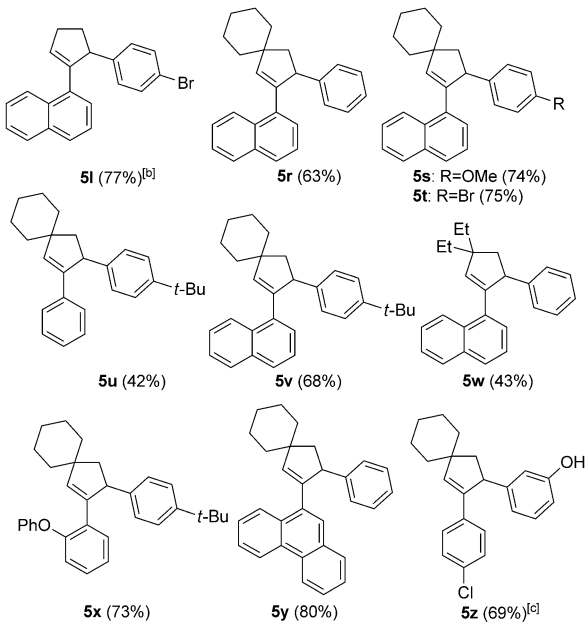
Scheme 2. Intramolecular formal (4+1) cycloaddition and its application to the preparation of a polyarene fragment.



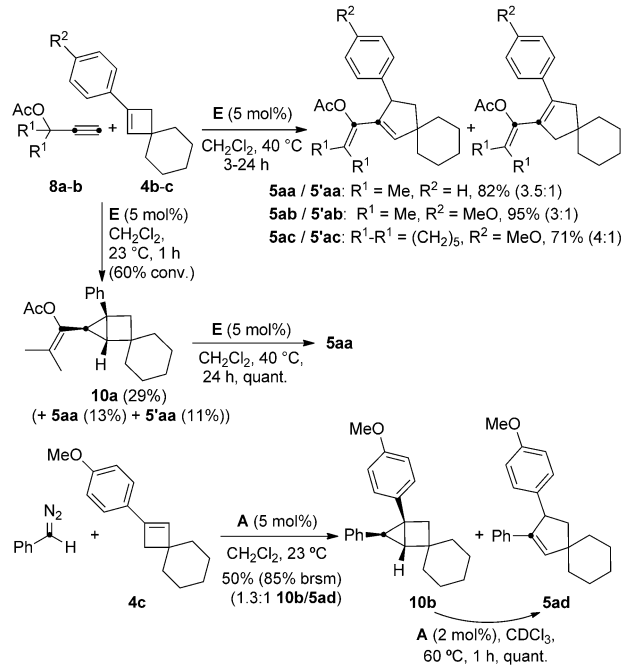
Scheme 3. Probing the mechanism of the formal (4+1) cycloaddition.

Table 3: Scope of the formal (4+1) cycloaddition between cycloheptatrienes **1** and cyclobutenes **4**.[a]





[a] Reaction at 120 °C, 0.2 M in 1,2-dichloroethane, 2 equiv of **4a–g**, catalyst **A** (5 mol%), 3 h. Yields are for isolated adducts. [b] Cyclobutene **4a** was isolated from the reaction mixture of **1a** and **3g**. [c] 2 Equiv of 7-(4-chlorophenyl)cyclohepta-1,3,5-triene were used.

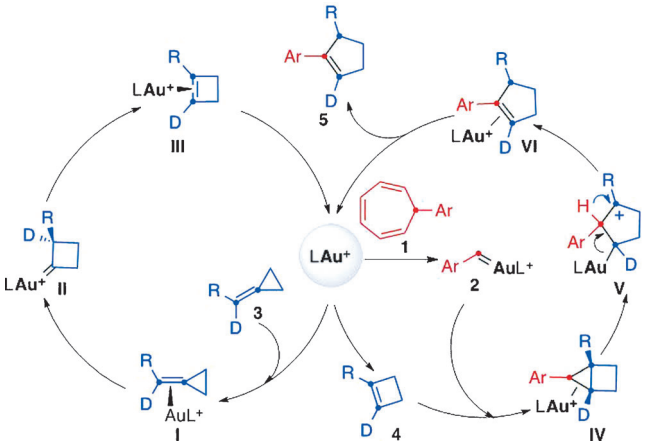


Scheme 4. Formal (4+1) cycloaddition with various gold-(I) carbenes.

Scheme 5. Deuterium labeling experiment to probe the mechanism.

To shed additional light on the reaction mechanism, we performed the reaction of cycloheptatriene **1a** with MCP [D_1]-**3a** in the presence of catalyst **A** (Scheme 5). In this experiment, [D_1]-**5a** was obtained with the deuterium label transferred completely to C-3.

According to all experimental data, we propose a mechanism for this formal (4+1) cycloaddition of cycloheptatrienes **1** and MCP in which gold(I) plays a triple role (Scheme 6). In the first catalytic cycle, η^2-MCP-gold(I) complex **I** undergoes ring expansion to form intermediate **II**, which gives η^2-cyclobutene-gold(I) complex **III**. Associative ligand exchange with the 7-aryl-1,3,5-cycloheptatriene, followed by retro-Buchner reaction then leads to the highly reactive gold(I) carbene **2**,[7] which reacts with cyclobutene **4** to form bicyclo[2.1.0]pentane-gold(I) complex **IV**. Cyclopropane opening by gold(I) forms the tertiary carbocation **V**, which leads to complex **VI** by a final 1,2-H shift. The cyclopropanation of **4** by **2**, followed by electrophilic cleavage probably follows a pathway similar to that occurring in the gas phase for the cyclopropanation/retro-cyclopropanation of enol ethers with gold(I) carbenes.[22] Formation of cyclopentenes from bicyclo[2.1.0]pentanes, the presumed intermediates of these reactions, has been mechanistically examined in a few cases using Rh^I, Zn^{II}, and other catalysts.[23,24] Formation of regioisomeric 3-alkyl-3-arylcyclopent-1-enes



Scheme 6. Proposed mechanism for the formal (4+1) cycloaddition.

together with **5n–p** in the reaction of alkyl-substituted MCP can be explained by the competitive migration of the aryl group in intermediates **V**.

In summary, we have developed a synthesis of substituted cyclopentenes by a formal (4+1) cycloaddition from methylenecyclopropanes or cyclobutenes with gold(I) carbenes generated under catalytic conditions by retro-Buchner reaction of 1,3,5-cycloheptatrienes or by other methods. Further work on the application of this cycloaddition in synthesis is underway.

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Keywords: (4+1) cycloaddition · carbenes · cyclobutenes · gold catalysis · methylenecyclopropanes

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